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MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS

42 Votsi Street, Patras 26221, Greece
Tel: +30 2610 279579, Fax: +30 2610 220518
email: iede_pel@yahoo.gr

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Editor-in-Chief
Christos Triantos
email: achaiki.iatriki@gmail.com

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ACHAIKI IATRIKI

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CONTENTS

Dear colleagues,

In the current issue, the editorial by Mastorogianni et al. summarizes the emerging therapeutic strategies for celiac disease that go beyond the traditional gluten-free diet, emphasizing novel pharmacological and immunological approaches targeting various aspects of disease pathophysiology. The editorial by Efthymiou et al. highlights the current role of colistin in the management of multidrug-resistant Gram-negative infections, focusing on its pharmacologic profile, resistance trends, clinical applications, and place in therapy amid emerging treatment options.

The current issue features three review articles. The first, authored by Efthymiou et al., provides an overview of the diverse causes and histopathologic patterns of granulomatous lymphadenopathy, emphasizing its diagnostic significance and clinical relevance as a histologic finding that can guide the identification of underlying infectious and non-infectious diseases. The review by Papasotiriou et al. presents contemporary data on the safety and risk of developing of acute kidney injury after the administration of iodinated contrast agents, as well as the risk of developing nephrogenic systemic fibrosis after exposure to gadolinium-based contrast media. Finally, the review by Tsoupra S. outlines the current understanding, diagnostic strategies, and management principles for elevated aminotransferases, highlighting their clinical significance and the importance of a structured approach to identifying underlying hepatic and extrahepatic causes.

Lastly, this issue features a case report by Bousis et al., which discusses the complications of invasive meningococcal disease, their management, and their impact on the overall prognosis of individuals with meningococcal sepsis.

Yours sincerely,

C. Triantos
Associate Professor in Internal Medicine
and Gastroenterology Faculty of Medicine,
School of Health Sciences, University of Patras
Editor-in-Chief of the journal "ACHAIKI IATRIKI"

Fighting Celiac Disease from Different Aspects: New Approaches to Treatment beyond the Gluten-free Diet

Ioanna Nefeli Mastorogianni, Fotios S. Fousekis, Konstantinos H. Katsanos

INTRODUCTION

Celiac disease (CeD) is an immune-mediated enteropathy occurring in genetically predisposed individuals carrying variants of the human leukocyte antigen (HLA) DQ2 and DQ8 genes. Its global prevalence rate is approximately 1.4% [1]. It is characterized by intestinal wall inflammation and malabsorption resulting from dietary intake of gluten proteins found in wheat, rye, and barley. These peptides cross into the submucosa, where they undergo deamination by tissue transglutaminase and bind to HLA-DQ2 or HLA-DQ8 on antigen-presenting cells, triggering T-cell activation. This immune response leads to infiltration of the epithelium and lamina propria by chronic inflammation cells and destruction of the intestinal villi [2].

Clinically, CeD is classified as classic, atypical, subclinical, potential, latent or refractory. It typically presents with malabsorption and symptoms such as abdominal pain, flatulence, steatorrhea, and weight loss. However, up to 50% of patients exhibit an atypical clinical presentation, with extraintestinal manifestations such as anemia, osteopenia, osteoporosis, arthralgia, menstrual cycle disorders, infertility, neuropsychiatric disorders, enamel tooth hypoplasia, alopecia, herpetic dermatitis, childhood growth retardation, etc.

Diagnosis requires a combination of serological, histological, and clinical findings, while treatment involves lifelong exclusion from gluten from the diet and a nutritious diet to meet the needs of the body [3].

The lack of effective pharmacological treatments for CeD is primarily attributed to the complexity of its pathogenesis, and the challenge of identifying an optimal target to address the multifaceted needs of patients. In this editorial, we primarily review current experimental therapies targeting various pathological aspects of the disease.

Therapy strategies beyond gluten-free diet

The various tested therapies that have emerged at the scientific forefront in recent years, intending to improve the quality of life of patients with gluten intolerance, could be categorized according to their therapeutic strategy and the specific point of the pathophysiological pathway they target.

A. Reducing Gluten Immunogenicity

Reduction of gluten immunogenicity has been achieved through genetic modification of gluten-containing foods. An example is the E82 wheat line, which is produced by RNAi technology that blocks relevant gliadin genes [4]. Pretreatment of flours or sourdoughs with microbial transglutaminase and N-methyl-lysine, or with probiotic bacteria of the genus Lactobacillus

Abbreviations: *CeD, Celiac disease; HLA, Human leukocyte antigen; tTG, tissue Transglutaminase; TG2, Transglutaminase II; IL-2, Interleukin 2; IFN-γ, Interferon γ; IL-17, Interleukin 17; IL-15, Interleukin15; mAb, monoclonal Antibody; IL-23, Interleukin 23.*

Key words: *Celiac disease; enzymatic degradation; immunomodulation; gut permeability; novel therapies*

Department of Gastroenterology and Hepatology, School of Health Sciences, University General Hospital of Ioannina, University of Ioannina, Ioannina, Greece

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(VSL#3), produces tolerable predigested gliadins without immunogenic peptides [5,6].

Transglutaminase II (TG2) inhibitors prevent the degradation of gluten peptides to form immunogenic complexes by inhibiting tissue transglutaminase activity. As a result, gluten-induced T-cell activation in the intestinal mucosa is reduced. Furthermore, TG2 inhibition has been shown in vitro to regulate intestinal epithelial permeability functions [7]. In a proof-of-concept trial, patients who received a six-week treatment with ZED1227, a selective oral TG2 inhibitor at a dosage of 100 mg, demonstrated significant improvement in symptoms and quality-of-life scores when compared to placebo [8].

AGY-010, an egg yolk anti-gliadin polyclonal antibody, and BL-7010 Copolymer P (HEMA-co-SS), which interacts with α-gliadin, are molecules that achieve gluten binding in the intestinal lumen. Specifically, AGY-010 neutralizes gluten proteins, preventing their degradation into immunogenic peptides. Results regarding the safety and efficacy of AGY capsules from a Phase 2 randomized, double-blind, placebo-controlled, crossover trial, are pending (NCT03707730) [9].

Gluten digestion through exogenous peptidases such as AN-PEP, Latiglutenase and Zamaglutenase, is another neutralization strategy. Latiglutenase (formerly known as ALV003) combines two gluten-specific recombinant proteases and is the most investigated molecule in human trials. In summary, the results of the studies suggest that ALV003 has the potential to mitigate the symptoms and histological damage caused by gluten, particularly in patients with positive serological markers [10]. Zamaglutenase (formerly known as TAK-062) is a computer-designed endopeptidase that targets the proline-glutamine dipeptide and has been shown to degrade over 99% of gluten in complex meals in both in vitro and Phase 1 in vivo studies [11]. AN-PEP is an Aspergillus Niger prolyl endoprotease that degrades into non-immunogenic residues, gluten and gluten peptides ingested with food [12]. Currently, several over-the-counter digestive enzyme supplements such as GliadinX, GluteZym and GluteoStop, are available, the effectiveness of which is controversial [12]. The results from the clinical studies on the efficacy of AN-PEP compared to placebo showed no significant differences in terms of worsening of CeD-related quality scores or antibody titers [13].

TIMP-GLIA (formerly TAK-101) is a nanoparticle for gliadin presentation. It induced sustained unresponsiveness to gluten in mice and showed inhibition of cytokines IL-2, IFN-γ, and IL-17, as well as reduced secretion of gliadin-stimulated T cells. In a Phase II trial, a 14-day gluten challenge in 33 patients showed an 88% reduction in IFN-γ spot-forming units compared to placebo.

B. Modification of the immune response

Inhibition of T-cell activation through HLA-DQ blockage is another therapeutic strategy. A multispecific antibody, DONQ52, was recently tested in HLA-DQ2.5+ patients (N=44) after a three-day grain challenge. DONQ52 inhibited the wheat gluten-specific T-cell response and reduced barley hordein and rye secalin T-cell responses [14].

Modifying the migration of gut-tropic lymphocytes to the intestinal mucosa is an alternative approach. Vercirnon (a CCR9 antagonist) and α4β7 integrin antagonists, such as Vedolizumab and PTG-100, could be useful for treating subsets of CeD patients. Results from Phase Ib and Phase II trials for PTG-100 and Vercirnon, respectively, are awaited [15].

Interleukin-15 (IL-15) is a critical component in the activation of intraepithelial lymphocytes and natural killer cells in CeD patients. PRN-015 (formerly AMG714), a humanized IgG1 anti-IL15 monoclonal antibody (mAb) and Hu-Mik-β1, an anti-IL15Rβ1 mAb, are currently undergoing Phase I testing in patients with refractory CeD [16]. Tofacitinib, a pan-JAK inhibitor, has demonstrated the potential to reverse the pathological manifestations of IL-15 overexpression, as evidenced in a transgenic celiac mouse model study [15].

Other immunomodulatory agents that have been used off label in isolated refractory cases are infliximab, an anti-TNFα agent, and rituximab, an anti-CD20 mAb. In some cases, symptomatic improvement has been observed, but larger randomized trials are lacking [17]. Budesonide, an oral glucocorticoid, has been studied in patients with both refractory and non-refractory CeD, possibly conferring clinical benefit while achieving better tolerance compared to systemic corticosteroids [14].

C. Induction of immunetolerance

Nexvax2 is a desensitizing vaccine with three gluten peptides, based on the immunotolerant training of CD4+ T lymphocytes through targeted gluten epitopes. Although in a Phase I clinical trial, Nexvax2 was well tolerated in HLA-DQ2+ patients, Phase II trial (RESET CeD) was discontinued due to lack of efficacy [18].

KAN-101 is based on the coupling of gluten immunogenic peptides to erythrocytes. It harnesses natural

tolerance through hepatic degradation, by activating Tregs, reducing the inflammatory response following gluten challenge. It is currently being evaluated in Phase Ib/II and Phase II trials [16].

Controlled parasitic infection with Necator americanus aims to suppress gluten-induced expansion of IFN-γ, IL-17, and IL-23, through intestinal immune homeostasis. Although results from a Phase I/II study showed no significant histological changes, further investigation in celiac patients experiencing occasional gluten exposure is needed [14].

D. Modulation of the interaction between gluten and epithelium

An alternative approach entails the reinforcement of the intestinal barrier, intending to prevent gluten translocation and the subsequent immune activation. One of the most studied agents is larazotide acetate (AT1001), a zonulin inhibitor that modulates tight junction integrity, reducing paracellular gut permeability. Despite the demonstrable efficacy and safety of larazotide in treating patients with persistent disease in a Phase IIb trial, Phase III trial was halted due to limited patient sample [19].

IMU-856 is an orally available small molecule that epigenetically regulates epithelial regeneration. Acting via upregulation of SIRT6, a sirtuin family protein involved in chromatin remodeling and transcriptional control of genes, maintains intestinal barrier function and promotes epithelial restoration of villous architecture [19]. In a Phase Ib trial that incorporated a 15-day gluten challenge, IMU-856 exhibited favorable outcomes in comparison with placebo. A reduction in gluten-induced mucosal damage was found based on measurements of the height of villi. Furthermore, IMU-856 improved or reversed disease-related symptoms, including bloating and fatigue [20].

CONCLUSIONS

In conclusion, the emergence of a variety of therapeutic strategies beyond the gluten-free diet represents a significant development in the management of CeD. These investigational agents target various aspects of CeD pathophysiology, ranging from enzymatic gluten degradation to immune modulation and intestinal barrier repair. The complexity and variability of CeD indicates the potential need for a personalized therapeutic approach, and the development of new treatments may contribute to this goal.

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Corresponding author:

Konstantinos H. Katsanos, MD, PhD, MPH, MBA, FEBGH,
Professor of Gastroenterology, Division of Gastroenterology,
Department of Internal Medicine,
Faculty of Medicine, University of Ioannina School
of Health Sciences, 45110 Ioannina, Greece
Tel.: +30 6947189157, E-mail: khkostas@hotmail.com

The role of Colistin against Multidrug Resistant Gram-Negative Bacteria in the Current Era

Dimitrios Efthymiou[1,2], Karolina Akinosoglou[1,2,3]

Colistin (polymyxin E), along with polymyxin B, were discovered back in the 1940s. Both were initially withdrawn due to neurotoxicity and nephrotoxicity but were reintroduced in the 1990s to treat multidrug-resistant gram-negative bacilli (MDR-GNR), including carbapenem-resistant *Enterobacteriales* (CRE), *Pseudomonas aeruginosa* (CRPA), and *Acinetobacter baumannii* (CRAB), when no other effective options were available [1].

Colistin kills bacteria primarily by disrupting the bacterial membrane through electrostatic and hydrophobic interactions with lipopolysaccharide (LPS). It has a narrow spectrum, mainly targeting gram-negative bacteria. It is effective against Enterobacteriaceae (e.g., *Citrobacter*, *E. coli*, *Salmonella*, *Shigella*, *Klebsiella*) and non-fermenters like *Acinetobacter*, *Pseudomonas aeruginosa*, and most *Stenotrophomonas maltophilia* strains. However, most anaerobes, gram-positive bacteria, gram-negative cocci (e.g., *Neisseria*), and pathogens such as *Moraxella catarrhalis*, *Helicobacter pylori*, *Proteus mirabilis*, *Pseudomonas mallei*, *Serratia marcescens*, and *Burkholderia cepacia* are intrinsically resistant to colistin.

Although polymyxins exhibit potent bactericidal activity against many gram-negative (GNR) bacteria, their extensive use has led to the emergence of resistant strains through different pathways, mainly driven by structural modifications of LPS in the bacterial cell. The mcr gene on bacterial plasmids facilitates this primary resistance mechanism. Studies conducted in two Greek hospitals reported a significant increase in colistin resistance, from <3.5% before 2010 to >20% after 2010 [2]. Interestingly, an increase in colistin use by one Defined Daily Dose (DDD) per 100 patient-days was associated with a 0.05 increase in the incidence rate of colistin resistance [3].

Colistin demonstrates rapid bactericidal activity against susceptible strains, with concentrations above the MIC leading to rapid killing even within five minutes following exposure, exhibiting a modest post-antibiotic effect. The free-drug area under the concentration-time curve to MIC ratio (fAUC: MIC) is considered the best PK/PD index for the efficacy and antibacterial activity of colistin. Commonly recommended doses, expressed in terms of colistin base (CBA) are 2.5-5 mg/kg/day divided q6-12hr IV/IM; not to exceed 5 mg/kg/day (milligrams of CBA) with a conversion factor of 1 million IU ~33 mgCB [1,2,4,5]. Therapeutic drug monitoring (TDM) is recommended for colistin, whenever possible, since doses cannot be safely optimized using clinical observation and dosing algorithms alone. Plasma concentrations required for antibacterial effect overlap with those associated with acute kidney injury, making the therapeutic window extremely narrow [5]. The most common side effects include nephrotoxicity (6-55%) and neurotoxity (7%), with both being dose-dependent and reversible on discontinuation of treatment [1,3,5].

[1]Department of Medicine, University of Patras, 26504, Patras, Greece
[2]Department of Internal Medicine, University General Hospital of Patras, 26504 Patras, Greece
[3]Division of Infectious Diseases, University General Hospital of Patras, 26504 Patras, Greece

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According to CLSI, the MIC break points for colistin are defined as ≤2 μg/ml for susceptibility and ≥4 μg/ml for resistance in *Pseudomonas aeruginosa* and *Acinetobacter* spp; no breakpoints are set for Enterobacteriaceae. EUCAST defines susceptibility as ≤2 μg/ml and resistance as >2 μg/ml for *P. aeruginosa*, *Acinetobacter* spp., and Enterobacteriaceae [2,5].

In the presence of new β-lactam/β-lactamase inhibitors (BL/BLIs), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) guidelines on the management of MDR -GNR pathogens give a conditional recommendation for the use of colistin against CRAB, CRE or CRPA, following available clinical evidence [6,7].

Carbapenem-resistant Enterobacterales (CRE)

In a retrospective clinical trial including 109 patients with carbapenem-resistant *Klebsiella pneumoniae* bacteraemia, 50% of whom in the intensive care unit (ICU), ceftazidime-avibactam (CAZ-AVI) treatment was associated with higher rates of clinical success while aminoglycoside and colistin-containing regimens were associated with increased rates of nephrotoxicity [8]. Similarly, monotherapy with meropenem–vaborbactam for CRE infection was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with best available therapy (BAT) including polymyxin alone or in combination (47%) [9]. In the case of imipenem/relebactam, a 28-day favourable clinical response and mortality was noted in 71% versus 10% and 40% versus 30%, among 47 patients who received imipenem/relebactam versus 16 colistin+imipenem, respectively [10]. According to the ESCMID guidelines, the use of meropenem-vaborbactam or CAZ-AVI for severe infections due to CRE, and the use of cefiderocol in case of CRE carrying metallo-b-lactamases and/or resistant to all other antibiotics are suggested. For non-severe infections caused by CRE, and in alignment with antibiotic stewardship principles, the use of an older antibiotic, that shows *in vitro* activity may be considered on a case-by-case basis, taking into account the site of infection [6].

Whether polymyxins should be used as monotherapy or in combination therapy for CRE infections remains controversial. Combination therapy appears to be beneficial, as polymyxins alone have notable limitations, including unpredictable plasma concentrations at the infection site, restricted dose escalation due to a narrow therapeutic window, and the risk of resistance development with monotherapy. Mechanistically, polymyxins can enhance synergy by increasing membrane permeability, thereby boosting intracellular concentrations of co-administered antibiotics [5].

A 2010 study by Michalopoulos et al. involving 11 ICU patients with CRE infections reported an 18.2% mortality rate using fosfomycin combined with colistin, gentamicin, or piperacillin/tazobactam, highlighting the potential of fosfomycin–colistin therapy despite the small sample size [11]. For invasive CRE infections, colistin is strongly recommended in combination with at least one agent with a susceptible MIC; if none are available, combine with one or more agents showing the lowest MICs, even if non susceptible [5]. In severe CRE infections susceptible only to polymyxins, aminoglycosides, tigecycline, or fosfomycin, or when new BL/BLIs are unavailable, combination therapy with two or more active agents, including meropenem (if MIC ≤8 mg/L and no BL/BLI is used), is recommended [6].

Pseudomonas aeruginosa

In the case of *P. aeruginosa*, a multicenter retrospective study on the use of ceftolozan/tazobactam (C-T) in 35 patients infected with CRPA showed a clinical success rate of 74%, mainly as monotherapy or in combination with agents such as colistin [12].

When combined with amikacin or colistin, greater overall reductions in MDR *P. Aeruginosa* bacterial burden are noted, particularly against those strains that were intermediate or resistant to C-T [13]. This aligns with *in vivo* studies highlighting the potent synergy of colistin with other drugs against *P. aeruginosa* [14].

In a multicentre, observational, prospective study in 11 ICUs including patients with bacteraemia and VAP by carbapenemase-associated *K. pneumoniae* and CRPA, treatment with fosfomycin plus mainly colistin or tigecycline reached a 54.2% clinical success by day 14 [14]. Nonetheless, a randomized controlled trial of 406 adults with severe carbapenemase resistant GNR infections (MIC >2 mg/L) susceptible to colistin (MIC ≤2 mg/L for *A. baumannii* and Enterobacteriaceae, ≤4 mg/L for *P. aeruginosa*) found no significant difference between colistin monotherapy and colistin–carbapenem combination therapy [15]. Given the limited and mostly observational data, the International Consensus Guidelines recommend combination therapy for invasive CRPA infections, using polymyxins with at least one agent showing a susceptible MIC. If no such agent is available, colistin should be combined with

one or more non susceptible agents, preferably those with the lowest MICs relative to breakpoints (e.g., a carbapenem) [5,7].

Acinetobacter baumannii

For CRAB infections, a recent meta-analysis of RCTs and observational studies in critically ill adults showed cefiderocol treatment was linked to lower 30-day mortality compared to other therapies, including colistin [16]. According to the 2024 IDSA guidelines, the preferred regimen against CRAB infections is sulbactam-durlobactam in combination with acarbapenem (ie, imipenem-cilastatin or meropenem). However, polymyxins (or minocycline, tigecycline, or cefiderocol) remain a reasonable choice, as an alternative regimen with high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) when sulbactam-durlobactam is not available [17].

When considering combination regimens, recommendations for invasive infections caused by CRAB support the use of polymyxins with one or more additional agents to which the pathogen displays a susceptible MIC. Contrary to *P. aeruginosa* and CRE infections, polymyxin monotherapy is preferred to combination therapy for *A. baumannii,* when no susceptibility is displayed to a second agent [5]. Interestingly, colistin-glycopeptide combination (CGC) has been previously shown to be a protective factor against mortality when administered for more than five days and not associated with increased nephrotoxicity. This is likely due to its action on the outer membrane, enabling glycopeptides access to cell wall targets from which they are usually excluded, while it also led to colistin being active against other MDR GNB that were heteroresistant [18].

Intrathecal / intraventricular or inhaled administration has also been utilized in clinical practice in cases of MDR pathogens, where permeability and levels are poor. Local administration can lead to much higher concentrations in cerebrospinal and pulmonary fluid, respectively, compared to systemic administration, resulting in lower plasma exposure and reduced toxicity.

Inhaled Colistin

The use of nebulized colistin to reduce side effects and enhance treatment of MDR GNR respiratory infections, especially VAP, remains controversial. A meta-analysis of 373 patients showed inhaled colistin was well tolerated and achieved 71.3% microbiologic success, with a 33.8% mortality rate. However, most studies were retrospective with varied endpoints, confounding factors, and often lacked control groups. Its role as adjunctive or substitute therapy remains unclear, particularly as an adjunct to standard treatment [19]. Two recent meta-analyses found that adding inhaled colistin to intravenous therapy for nosocomial pneumonia or VAP significantly improved clinical outcomes, microbiological eradication, and reduced infection-related mortality, though overall mortality remained similar between groups [20]. The International Consensus Guidelines for the optimal use of the polymyxins, support that IV polymyxin therapy for suspected or documented XDR gram-negative HAP or VAP should be combined with adjunctive polymyxin aerosol therapy [5], even though, recent ESMID and IDSA guidelines do not support its use [6,17].

Intrathecal (ITH) and intraventricular (IVT) polymyxin

Colistin penetrates cerebrospinal fluid (CSF) poorly, reaching only about 5% of serum levels, but achieves 34–67% during meningitis. ITH and IVT colistin infusions are effective alternatives.

A systematic review of 234 cases of healthcare-associated ventriculitis or meningitis caused by GNR-pathogens and treated with once-daily ITH or IVT colistin showed an 85% success rate. Toxicity, including chemical ventriculitis or meningitis, occurred in 7% of cases. Guidelines recommend IVT or ITH polymyxins at 125,000 IU CMS (~4.1 mg CBA) daily, combined with IV polymyxin, for MDR and XDR gram-negative infections [5].

CONCLUSION

Overall, colistin is a narrow-spectrum antibiotic effective against several MDR and XDR GNR bacteria. It demonstrates synergy with rifampicin, carbapenems, and less commonly, vancomycin.

Despite the emergence of resistance to new BL/BLIs, colistin remains a valuable option against CRE and CRPA infections and should be considered for CRAB when sulbactam/durlobactam is unavailable. Evidence on alternative administration routes, such as inhalation or intrathecal/intraventricular, is limited. However, inhalation appears promising for step-down therapy or prophylaxis. Colistin must be used carefully, at the correct dosage, duration, and in combination with other agents, to minimize toxicity, curb resistance, and optimize clinical outcomes against MDR gram-negative infections.

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Corresponding author:

Karolina Akinosoglou MD, PhD
Internist-Infectiologist, Associate Professor, Department of Internal Medicine, University of Patras
Tel.: +30 2613603582, Rio, Patras, Greece, E-mail: akin@upatras.gr

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Granulomatous Lymphadenopathy: A non-specific yet useful finding to come across

Dimitrios Efthymiou[1], Pinelopi Bosgana[2], Leonidia Leonidou[1,3]

Abstract

Granulomatous lymphadenopathy, or more accurately granulomatous lymphadenitis (GLA), is a histologic pattern of tissue reaction, specifically granulomatous inflammation, in one or more lymph nodes of the human body. It is a type of chronic inflammation characterized by the local aggregation of inflammatory cells, typically organized in an oval-shaped formation. These cell aggregations primarily consist of T-cells, macrophages, epithelioid cells, and giant cells, which are activated by different antigens, leading to granuloma formation (epithelioid cell granulomas). A wide variety of conditions can lead to this reaction, which is encountered more often than expected during diagnostic workups. This underscores the importance of a pattern-based algorithmic approach, combined with the clinical context, to narrow down the pathologic and clinical differential diagnoses. Such an approach contributes to the subsequent clinical management of underlying entities, which may range from infections to malignancies.

Key words: *Granulomatous lymphadenitis; granuloma; lymphadenopathy; adenopathy; sarcoid like reactions*

Granulomatous Inflammation

Granulomatous inflammation is a type of inflammation that is often organized in an oval-shaped formation within tissues. It is characterized by a focal aggregation of inflammatory cells primarily histiocytes, macrophages, activated macrophages (epithelioid cells) and giant cells (foreign body or Langhans) along with small lymphocytes and plasma cells which typically surround the aforementioned cells [1].

This type of tissue reaction develops in response to persistent, non-degradable stimuli or as a result of hypersensitivity reactions. In most infectious diseases, these two mechanisms appear to overlap. Granulomas serve as a protective mechanism when acute inflammatory processes fail to eliminate causative agents. Their formation follows a stepwise series of events involving a complex interplay between immune cells, causative agents and biological mediators. These areas of inflammation or immunologic reactivity attract monocytes-macrophages, also known as histiocytes when present in tissues, which may fuse to form giant cells or lose their characteristic bean-shaped appearance to become activated epithelioid cells. The centre of the granuloma may occasionally exhibit necrosis [2].

Materials and Methods

Herein, we conducted a literature search in the PubMed database using the keywords 'Granulomatous lymphadenitis' or 'Granuloma' and 'Lymphadenopathy' or 'Granuloma' and 'Adenopathy' or 'Sarcoid Like Reactions'.

[1]Department of Internal Medicine, University Hospital of Patras, Patras, Greece
[2]Department of Pathology, General Hospital of Patras, Patras, Greece
[3]Division of Infectious Diseases, University Hospital of Patras, Patras, Greece

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Search was limited to articles written in English and published until February 2025. We ended up choosing 43 articles that were more relevant and concise, in order to keep the references credible but also easily accessible.

Granulomatous Lymphadenitis

Granulomatous lymphadenopathy (GLA), more accurately granulomatous lymphadenitis, is a histologic pattern characterized by granulomatous inflammation in one or more lymph nodes of the human body [3]. Histologically, it is characterized by the collection of epithelioid macrophages with eosinophilic cytoplasm and indistinct cell borders, surrounded by a rim of inflammatory cells (lymphocytes, plasma cells, macrophages) while multinucleated giant cells are often present.

Two main histological subtypes exist: necrotizing and non-necrotizing granulomas [4]. Necrotizing granulomas have a necrotic focus surrounded by a rim of chronic inflammatory cells, including epithelioid macrophages [5] (Figure 1, 2). Although it is not a specific pathological finding, histologic identification of granulomatous inflammation is a useful predictor of diagnostic etiology and can lead to a definitive diagnosis with the aid of ancillary testing, such as special stains and molecular diagnostics. This is because the specific histologic patterns of the granuloma (e.g., foreign-body, necrotizing, non-necrotizing, suppurative, etc.) can help narrow the clinical differential diagnosis when considered alongside the clinical context (Figure 3, 4).

Factors such as patient's age and ethnic background, the location of the affected lymph node [whether extracted surgically or sampled via fine-needle aspiration cytology (FNAC) or fine-needle aspiration biopsy (FNAB)], immune status, coexisting HIV infection, past medical history, presenting clinical features and physical examination findings all contribute to determining the underlying cause [3,6].

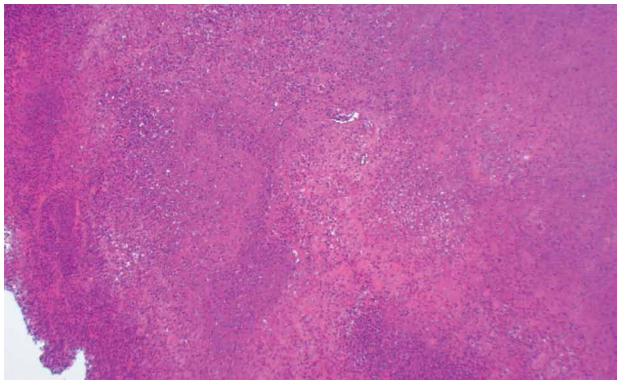

Figure 1. A 67-year-old patient with necrotic granulomatous lymphadenitis (x100).

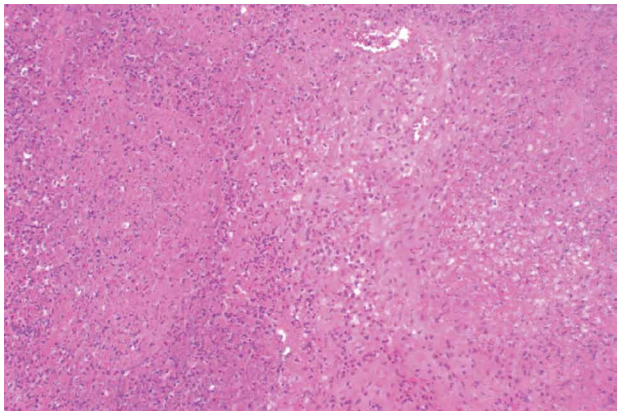

Figure 2: Necrotic areas surrounded by a rim of epithelioid histiocytes and lymphocytes in the sample of the lymph node (x200).

Histologic Subtypes

The term granulomatous inflammation encompasses a wide spectrum of histologic findings, ranging from well-defined granulomas to loose collections of histiocytes mixed with other inflammatory cells. The latter is typically observed in chronic tissue injury and healing processes. While the loose type is non-specific, well-defined granulomas can offer potential diagnostic insights.

Two forms of well-defined granulomas exist, classified by their etiology: foreign-body giant cell granulomas and immune granulomas. Foreign-body granulomas result from a reaction to inert materials without an adaptive immune response, whereas immune granulomas arise from various etiologies.

Histologically, foreign-body granulomas present as collections of histiocytes surrounding foreign material. Immune granulomas, on the other hand, can be further characterized as necrotizing or non-necrotizing ("naked"). This classification depends on the presence or absence of central necrosis with a palisaded lymphohistiocytic reaction and a surrounding cuff of chronic inflammation. A specific subtype of necrotizing granuloma, in which the central necrotic material has a "cheese-like" consistency, is referred to as caseous necrosis [3].

Additionally, suppurative granulomatous inflammation is another histologic pattern, defined by the presence of epithelioid histiocytes and multinucleated giant cells with a central collection of polymorphonuclear leukocytes (PMNs). It may be associated with both

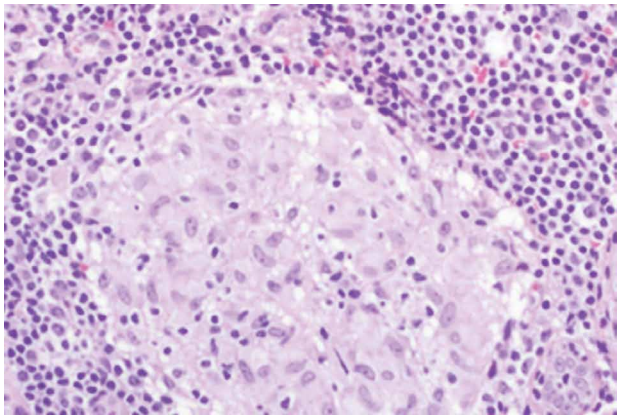

Figure 3. Non necrotizing granuloma.

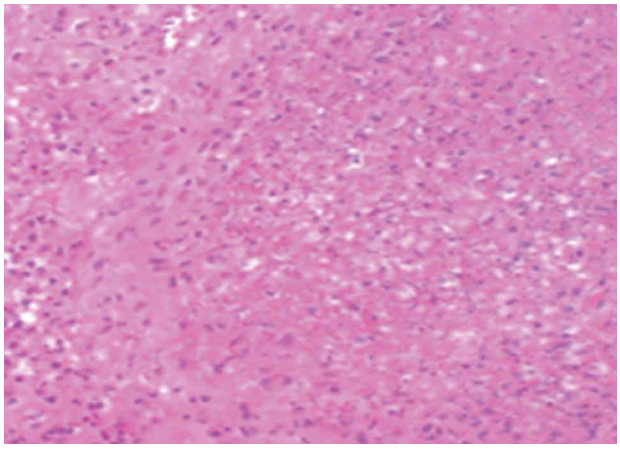

Figure 4. Necrotic debris in a necrotizing granuloma.

necrotizing and non-necrotizing granulomas. Based on light microscopy alone, suppurative granulomatous inflammation (SGI) represents the end process of various infectious diseases [7].

Lymph Node Biopsy

When obtaining a lymph node biopsy, excisional biopsy remains the gold standard, as it better preserves lymph node architecture and provides sufficient tissue to perform ancillary studies, including microbiologic testing, special stains and immunohistochemistry [8]. However, a 16-year retrospective review by Ng, D. L., & Balassanian, R. analyzing 339 FNABs diagnosing granulomatous inflammation (59% of which involved lymph nodes), demonstrated that FNAB is an excellent, minimally-invasive technique that allows for critical ancillary testing necessary for a definitive diagnosis [9].

CLASSIFICATION & ETIOLOGY OF GRANULOMATOUS LYMPHADENITIS (GLA)

Granulomatous lymphadenitis is broadly classified into two categories: infectious and non-infectious GLA. Based on histological appearance, granulomas can be further subclassified as necrotizing or non-necrotizing, caseous or non-caseous, and suppurative or non-suppurative [3,5] (Table 1).

A) Non-infectious GLA

Non-infectious causes of GLA include sarcoidosis and sarcoid-like reactions, which encompass a range of diseases that can mimic sarcoidosis both histologically and clinically [10]. Conditions associated with sarcoid-like reactions include:

- Occupational exposure diseases (e.g., silicosis, berylliosis)
- Lymph nodes draining neoplasms
- Lymphomas (Hodgkin's and non-Hodgkin's)
- Drug-induced sarcoidosis-like reactions (DISRs)
- Lymph nodes draining areas affected by Crohn's disease, vasculitis, and other diseases [5]

B) Infectious GLA

Infectious GLA is further classified as suppurative or non-suppurative:

1. Suppurative GLA:

- Characterized by early follicular hyperplasia and sinus histiocytosis.
- Associated with tularemia lymphadenitis, cat scratch disease (CSD), Yersinia lymphadenitis, fungal infections, and lymphogranuloma venereum.
- In tularemia and CSD, monocytoid B lymphocytes (MBLs), T cells, and macrophages contribute to granuloma formation. However, in epithelioid cell granulomas of Yersinia lymphadenitis, MBLs are absent, unlike in CSD.
- Notably, almost all granulomas induced by Gram-negative bacteria contain a central abscess.

2. Non-Suppurative GLA:

- Includes hypersensitivity-type granulomas caused by:
  - Mycobacterium tuberculosis
  - Atypical mycobacterium infections
  - Bacillus Calmette-Guérin (BCG) lymphadenitis
  - Toxoplasma lymphadenitis (Piringer-Kuchinka lymphadenopathy)
  - Leprosy, syphilis, and brucellosis

Table 1. *Granulomatous Lymphadenitis classification, causes, histological findings and lymph nodes most commonly affected.*

Types of Granuloma		Histological characteristics	Lymph nodes affected
NON-INFECTIOUS		Rarely have abscesses and necrosis in the center	
A. Sarcoidosis		**Non-caseous** epithelioid granulomas with characteristic sharp demarcation, lack of central **necrosis** and special staining, such as acid-fast and silver impregnation staining	Pulmonary hilar lymph nodes (93.5%), cervical (12.2%), axillary (5.2%) and inguinal (3.3%) lymph nodes
B. Sarcoid Like Lymphadenitis			Regional lymph nodes
	I. Malignancies	**Non caseating** epithelioid cell granulomas contain B cell lymphocytes and sinus histocytes that are not typically observed in sarcoid granulomas	Regional and distal lymph nodes
	Lymphoma Hodgkin and non-Hodgkin)		
	Sarcoidosis-like reaction of malignancy		
	II. Crohn's disease	Not well-formed, non-caseous	Intestinal lymph nodes (draining)
	III. Vasculitis		
	GPA	Loosely formed granulomas with multinucleate giant cells, necrotic debris, and abundant PMN	
	EGPA	Loosely formed granulomas with necrotic debris and eosinophils	
	IV. Occupational-environmental exposure		
	Silicosis	Granulomatous inflammation with focal necrosis	Subcarinal, mediastinal and hilar
	Berylliosis	Non-necrotizing granulomas (identical to sarcoidosis)	Hilar and mediastinal lymph nodes.
	V. Drug Induced Sarcoidosis like reactions (DISRs)	Granulomas completely resemble sarcoid granulomas with presence of non-caseating giant-cell epithelioid granulomas surrounded by lymphocytes, with occasional presence of birefringent foreign bodies, asteroid bodies and Schaumann	Hilar
	VI. Other diseases		
	Primary Biliary Cirrhosis (PBC)	Epithelioid non suppurative granulomas	Any
	Adult onset Stills Disease (AOSD)	Suppurative necrotizing granulomatous lymphadenitis	Mesenteric lymph nodes

Table 1. *Granulomatous Lymphadenitis classification, causes, histological findings and lymph nodes most commonly affected.*

Types of Granuloma		Histological characteristics	Lymph nodes affected
INFECTIOUS			
A. Suppurative		Follicular hyperplasia and sinus histiocytosis (early phase) - Almost all Gram-negative bacteria induced granulomas have central abscesses and necrosis	
	I. Tularemia Lymphadenitis	Monocytoid B lymphocytes (MBLs) with T cells and macrophages Three phases: • Abscess phase: lymph follicles and histiocytic cells in subcapsular sinus. • Abscess with central necrosis and mononuclear cells • Abscess-granulomatous form: small granulomas with central necrosis at the cortex and the paracortex that fuse and form irregular large lesions • Granulomatous form: Necrosis is homogenized-caseous necrosis	Axillary and cervical
	II. Cat scratch Lymphadenitis	Monocytoid B lymphocytes (MBLs) with T cells and macrophages. Three phases: • Early phase (of non-specific reactivity): Reactive follicular hyperplasia, histiocytic proliferation and expansion of lymphoid follicles • Intermediate phase (micro-abscess formulation): Micro-abscesses with centric necrosis, clustered neutrophils, lack of epithelioid granuloma within the sub-capsular sinus. Centric fibrinoid necrosis is comprised of neutrophilic aggregates and progressive suppuration • Final phase: Epithelioid cell granulomas configured by Enveloping macrophages within frequent multinucleated or Langhans giant cells (stellate micro-abscess). Integration of the stellate micro-abscesses of varying magnitude produces an irregular, giant abscess (geographic abscess)	Axillary, inguinal and cervical

Table 1. *Granulomatous Lymphadenitis classification, causes, histological findings and lymph nodes most commonly affected.*

Types of Granuloma		Histological characteristics	Lymph nodes affected
	III. Yersinia Lymphadenitis	NO MBLs in the epithelioid cell granulomas • Yersinia enterocolitica lymphadenitis: Non-suppurative epithelioid cell granulomas in the germinal centres but suppuration of the centric epithelioid cell granulomas may ensue (central micro-abscesses) and expand to spheroid micro-abscesses. Composed of epithelioid histiocytes along with dispersed, miniature lymphocytes and plasmacytoidmonocytes • Yersinia pseudotuberculosis: Intense neutrophilic infiltrate and miniature granulomas with subsequent, disseminated micro-abscesses, centric suppuration and an envelope of histiocytes (Suppurative granulomas)	Mesenteric (lymph nodes of the ileum and cecum)
	IV. Lymphogranulomavenerum	Miniature necrotic locus with neutrophilic infiltration →expansive, necrotic foci →stellate micro-abscesses	Inguinal
	V. Fungal infection	Suppurative or non-suppurative granulomas. The fungal organism may be demonstrated by the Grocott's Methenamine Silver (GMS) and Periodic acid Schiff (PAS) Gridley stains	Any
A. Non Suppurative			
	I. Tuberculous Lymphadenitis	From multiple, miniature epithelioid cell granulomas resembling sarcoid granulomas, to massive caseous necrotic aggregates enveloped by Langhans giant cells, epithelioid cells and mature lymphocytes	Cervical and mediastinal (90%)- Ghon's complex
	II. Atypical Mycobacterial infections-Non Tuberculous Mycobacteria (NTM)	Well-formed granulomas with or without caseous necrosis / Typically necrotizing granulomas	
	III. BCG- Lymphadenitis.	Follicular hyperplasia and sinus histiocytes in the early phase / later: micronodules of epithelioid granulomas without necrosis and epithelioid cell granuloma with central coagulation necrosis / Langhans giant cells rarely appear	Axillary and cervical

Table 1. *Granulomatous Lymphadenitis classification, causes, histological findings and lymph nodes most commonly affected.*

Types of Granuloma		Histological characteristics	Lymph nodes affected
	IV. Toxoplasma Lymphadenitis (Piringer-Kuchinka lymphadenopathy)	Three characteristic features: florid follicular hyperplasia, small epithelioid granulomas (mainly at the follicular periphery) and dilated marginal and cortical sinuses with monocytoid B cells (MBLs). Necrosis and Langhans giants cells are rare	Immunologically competent: A limited, firm, moderate posterior cervical lymphadenopathy.
	V. Leprosy	Typically, not suppurative	Any
	VI. Syphilis	Typically, non-caseating	Any (typically in tertiary syphilis)
	VII. Fungal infection	Suppurative or non-suppurative granulomas. The fungal organism may be demonstrated by the Grocott's Methenamine Silver (GMS) and Periodic acid Schiff (PAS) Gridley stains	Any
	VIII. Brucellosis	Nonspecific follicular hyperplasia and aggregates of epithelioid cells to massive non-caseating granulomas	Any-Even isolated abdominal lymphadenopathy

- Fungal infections (e.g., Cryptococcus, Histoplasma, Coccidioidomycosis, Pneumocystis) may present with both suppurative and non-suppurative granulomas [5]

NON-INFECTIOUS GLA

A. Sarcoidosis

Sarcoidosis is a granulomatous, multisystem disease of unknown etiology affecting different organs such as the lungs, skin, kidneys, joints, muscles and eyes [5,11]. It occurs in individuals of all ethnic backgrounds with a higher prevalence in non-smokers, females, African Americans and Scandinavians and typically affects adults aged 30-50 years [11, 12].

Sarcoidosis is a highly heterogeneous disease with phenotypes ranging from acute to subacute and chronic forms. Many patients remain asymptomatic, but approximately 20% develop chronic progressive disease, potentially leading to lung fibrosis [12]. Mortality occurs in 2-4% of cases, primarily due to respiratory failure from pulmonary fibrosis, although cardiac involvement (e.g., sudden cardiac death) is also a rare but serious complication [12].

Clinical and Radiological Features

- Intrathoracic involvement is observed in 90% of patients typically presenting as bilateral hilar adenopathy and/or diffuse lung micronodules, along the lymphatic structures.
- Extrapulmonary manifestations occur in 25-50% of cases and include:
  - Skin lesions
  - Uveitis
  - Liver or splenic involvement
  - Peripheral and abdominal lymphadenopathy
  - Peripheral arthritis [11]
- Symptoms may range from mild (dry cough, low grade fever, fatigue, weight loss, arthralgia) to severe (Löfgren syndrome, Heerfordt-Waldenström syndrome, lupus pernio, erythema nodosum) [12].
- Hypercalciuria and hypercalcemia occur in ~10% of cases, resulting from increased external production of active vitamin D by macrophages in granulomas [13]. Diagnosis is confirmed when typical clinical and radiological findings are supported by histological evidence of non-necrotic granulomas and by the exclusion of possible alternative diagnoses, since it is a diagnosis of exclusion.

Diagnosis of Sarcoidosis

Sarcoidosis is a diagnosis of exclusion, requiring:

1. Compatible clinical and/or radiological findings

2. Histological evidence of non-necrotizing granulomatous inflammation
3. Exclusion of alternative causes of granulomatous diseases

In some cases (e.g., Löfgren or Heerfordt syndromes) a presumptive diagnosis can be made without a tissue biopsy [11]. Lymphadenopathy is frequently observed, most commonly in pulmonary hilar lymph nodes (93.5%). Cervical (12.2%), axillary (5.2%), and inguinal (3.3%) lymph nodes may also be affected.

Granulomas of sarcoidosis can be distinguished from tuberculosis, fungal infection, silicosis, berylliosis, and Hodgkin's lymphoma, by their characteristic sharp demarcation, lack of central necrosis and special staining techniques, such as acid-fast and silver impregnation staining in combination with other clinical and laboratory findings [5].

Follicular hyperplasia and sinus histiocytosis may initially resemble nonspecific lymphadenitis. In early stages, these changes give way to well-demarcated granulomas composed of epithelioid cells with scattered multinucleated giant cells, eventually leading to fibrosis and hyalinization [5]. Numerous inclusion bodies may be identified within cytoplasm of giant cells, including:

- Asteroid bodies (composed of calcium, silicon, phosphorus and aluminum)
- Schaumann bodies (round, concentric laminations of iron and calcium)
- Calcium oxalate crystals
- Periodic acid-Schiff (PAS)-positive inclusions, which are yellow or ovoid bodies with uncertain etiology/pathogenesis [1]

B. Sarcoid Like Lymphadenitis

I. Malignancies

Sarcoid-like reactions (SLR) have been described not only with lymphoma [14] but with various solid and hollow organ malignancies including lung cancer [15], breast cancer [16], colorectal [17] and stomach cancer [18] and genitourinary cancers [19]. Although the clinical significance of SLR in cancer patients remains unclear, literature suggests that it is associated with more favorable outcomes [20].

Sarcoidosis-like reactions in malignancy are believed to result from a T-cell-mediated response to soluble tumor antigens, which may be shed by tumor cells or released due to tumor necrosis. These reactions lead to non-caseating epithelioid cell granulomas containing B-cell lymphocytes and sinus histocytes, which are not typically observed in sarcoid granulomas [10, 21].

Regarding sarcoid-like lymphadenitis associated with hematologic malignancies, it is more common in Hodgkin lymphoma than in non-Hodgkin lymphoma [14]. A careful histologic examination can usually confirm the diagnosis, potentially revealing Reed-Sternberg cells in cases of Hodgkin lymphoma. Additionally, lymphocyte marker analysis within the granulomas and ancillary studies may aid in establishing the diagnosis [10].

II. Crohn's Disease

Crohn's disease is a type of inflammatory bowel disease that can affect any part of the gastrointestinal tract and is characterized by skip lesions. Its onset is usually insidious, with clinical features depending on the location and behaviour of the disease (inflammatory, stricturing, or penetrating). The most common symptoms include abdominal pain, chronic diarrhoea (bloody or non-bloody) and weight loss.

Granulomas are present in 15% to 70% of Crohn's disease patients [22]. Histologically, these granulomas form in draining intestinal lymph nodes and tend to be less well-formed than those seen in sarcoidosis. They are typically non-caseating, which helps differentiate them from intestinal tuberculosis [1,22].

III. Vasculitis

Both granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) are types of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis characterized by systemic vasculitis and granulomatous inflammation in tissues [23]. Although not a common practice, a biopsy of affected lymph nodes in patients with clinical and serological evidence of vasculitis may aid in diagnosis.

Histopathological findings include:

- **GPA:** Loosely formed granulomas with multinucleated giant cells, necrotic debris and abundant polymorphonuclear neutrophils (PMNs)
- **EGPA:** Loosely formed granulomas with necrotic debris and eosinophils [24]

A diagnosis of EGPA is supported by a history of asthma, peripheral eosinophilia, and pulmonary, and renal involvement. In contrast, GPA is more likely if the histological findings are combined with upper respiratory tract, pulmonary, and renal involvement along with positive ANCA (PR3+) serology [24].

IV. Occupational-Environmental Exposure

Pneumoconiosis is a spectrum of parenchymal lung diseases caused by the inhalation of (usually) in organic dusts in occupational settings [25]. Silicosis, one of the most common forms, results from inhaling crystalline silica. The typical clinical presentation involves a history of silica exposure, diffuse interstitial opacities and nodules predominantly in the lung apices, often progressing to fibrosis. Lymphadenitis may also be a finding as described in a case by Faisal, Hafsa et al [26]. Pathological lymph nodes (subcarinal, mediastinal and hilar) were identified in that case with an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy revealing granulomatous inflammation with focal necrosis and polarized foreign material, suggestive of silica exposure [26].

Another occupational disease, berylliosis (chronic beryllium disease), is a cell-mediated hypersensitivity disorder caused by exposure to beryllium and beryllium alloys in industrial settings. It leads to non-necrotizing granulomas that are histologically indistinguishable from those of sarcoidosis. These granulomas can be present in pulmonary tissue as well as hilar and mediastinal lymph nodes [27].

V. Drug-Induced Sarcoid-Like Reactions (DISR)

A drug-induced sarcoidosis-like reaction (DISR) is a systemic granulomatous response that is difficult to differentiate from sarcoidosis. It typically occurs 4 to 24 months after the initiation of a new drug [10, 28].

Four major drug categories have been implicated in DISR:

1. Interferons
2. Highly active anti-retroviral therapy
3. Immune checkpoint inhibitors
4. Tumour necrosis factor alpha (TNF- α) antagonists [28]

The primary method for distinguishing DISR from sarcoidosis is the resolution of clinical findings after discontinuing the offending drug. Otherwise, the clinical manifestations of both conditions are similar.

Histopathologically, DISR granulomas closely resemble those of sarcoidosis, consisting of non-caseating giant-cell epithelioid granulomas surrounded by lymphocytes. Occasional birefringent foreign bodies, asteroid bodies, and Schaumann bodies may be present. The hilar lymph nodes are most commonly affected, similar to sarcoidosis [28].

Treatment may not be necessary if there are no significant clinical findings. However, if intervention is required, discontinuing the causative drug is the preferred approach. If discontinuation is not possible due to the drug's therapeutic benefits, standard anti-sarcoidosis regimens used in parallel with the drug may be effective [28].

VI. Other diseases

Primary Biliary Cirrhosis

Primary Biliary Cirrhosis (PBC) is a progressive non-suppurative granulomatous inflammation of the bile ducts, primarily affecting women of reproductive age [2]. Epithelioid granulomas may also be present in various lymph nodes, and PBC can mimic sarcoidosis both clinically and histologically [2, 29].

Adult-onset Still's disease (AOSD)

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology and pathogenesis. It is typically accompanied by lymphadenopathy in 65% of cases and is histologically associated with intense paracortical immunoblastic hyperplasia. However, literature references indicate that suppurative necrotizing granulomatous lymphadenitis has also been linked to AOSD. For example, Assimakopoulos et al (2012) reported a case of a young adult with mesenteric lymphadenitis associated with AOSD [30].

Kikuchi-Fujimoto Disease

Kikuchi-Fujimoto disease is a benign, self-limiting disorder of the lymphoreticular system with unknown etiology. It predominantly manifests as cervical lymphadenopathy in young women. However, histologically, it is characterized by histiocytic necrotizing lymphadenitis without any granulomas or caseation. Therefore, it should not be confused as a cause of granulomatous lymphadenopathy [31].

INFECTIOUS GRANULOMATOUS LYMPHADENITIS (GLA)

A. Suppurative Granulomatous Lymphadenitis

I) Tularemia Lymphadenitis

Tularemia (Ohara's disease) is a potentially fatal multisystemic disease affecting humans and animals. It is caused by the facultative intracellular Gram-negative bacterium *Francisella tularensis* [32]. *F. tularensis* is classified into three subspecies:

- *Tularensis* (mainly seen in North America)
- *Holarctica* (distributed from Europe to Japan)

- *Mediasiatica* (found in Central Asia)

Infection occurs through arthropod bites, direct contact with infected animal tissues (e.g., during hunting season from November to January) ingestion of contaminated food or water, and inhalation of infectious aerosols, making tularemia a potential bioterrorism threat [5].

Depending on the mode of transmission, tularemia can present in various forms, including ulceroglandular, glandular, oculoglandular (Parinaud oculoglandular syndrome), oropharyngeal, respiratory, and typhoidal [32]. The glandular and ulcerograndular forms are the most common, with skin ulcers appearing primarily on the upper extremities and fingers. Due to regional spread, axillary and elbow lymph nodes are most frequently affected [5]. Lymph node enlargement typically develops within one week after initial skin lesions [1].

Tularemia is characterized by the sudden onset of high fever (38-40ºC) headache, flu-like symptoms, and generalized pain, particularly back pain. It can lead to complications such as pneumonia, meningitis, sepsis, or even plaque-like symptoms when transmitted through ingestion.

Histopathologically, tularemia-associated lymphadenopathy progresses through three phases:

1. **Early (Abscess) Phase (Week 1)** – Lymph follicles appear, histiocytic cells gather in the subcapsular sinus, and abscesses with central necrosis form. MBLs are detected adjacent to these lesions.
2. **Abscess-Granulomatous Phase (Weeks 2-6)** – Small epithelioid granulomas with central necrosis fuse to form larger irregular lesions with central abscesses. CD4+ cells predominate over CD8+cells, and multinucleated giant cells appear at the periphery of the granulomas.
3. **Granulomatous Phase (After week 6)** – Necrosis becomes homogenous and may resemble caseous necrosis in the centre of the granulomatous lesion [5].

II. Cat Scratch Disease Lymphadenitis (CSD Lymphadenitis)

Cat scratch disease (CSD) is caused by the Gram-negative bacteria *Bartonella henselae* and *B. quintana,* typically following a cat scratch or bite. Many patients do not recall direct contact with a cat. The disease primarily affects immunocompetent children and adolescents, presenting with self-limited fever and painful, localized granulomatous lymphadenopathy (mainly axillary or inguinal or cervical) near the inoculation site. In rare cases, visceral, neurological, and ocular involvement can occur, particularly in immunocompromised individuals.

Immunocompromised patients, such as renal transplant recipients on long-term immunosuppressive therapy, are at risk for severe chronic infections like bacillary angiomatosis [1][33]. Rare cases of mediastinal lymphadenopathy associated with *Bartonella Henselae* have been reported and disseminated infection or endocarditis should be ruled out in such cases [34].

In immunocompetent patients, CSD is usually self-limiting with adenopathy resolving within 8 to 16 weeks. However, in immunosuppressed individuals, antimicrobial therapy is typically required [33].

Histopathologically CSD lymphadenitis progresses through three stages:

1. **Early phase**– Reactive follicular hyperplasia, histiocytic proliferation and expansion of lymphoid follicles.
   Intermediate Phase – Formation of micro-abscesses with central necrosis, containing clustered neutrophils but lacking epithelioid granulomas. Necrotic debris extends from the subcapsular sinus to the lymph node cortex. Centric fibrinoid necrosis comprises neutrophilic aggregates and progresses to suppuration. MBLs may also be seen.
2. **Late phase**–Formation of epithelioid cell granulomas, multinucleated Langhans giant cells, and *stellate micro-abscesses* that eventually coalesce into large irregular geographic abscesses [1].

III. Yersinia Lymphadenitis

Yersinia enterocolitica and *Yersinia pseudo-tuberculosis* are Gram-negative bacilli from the *Enterobacteriaceae* family that cause yersiniosis. Following ingestion of the contaminated food or water, the bacteria colonize the distal intestine and spread to mesenteric lymph nodes via lymphatic vessels, leading to various abdominal manifestations, including gastroenteritis, ileitis, and mesenteric lymphadenitis [35].

Clinical symptoms include diarrhea (80%), right lower quadrant pain (50%), nausea, vomiting, fever (38-39˚C), and flu-like symptoms that can mimic acute appendicitis, occasionally leading to unnecessary surgery.

Histopathologically, *Yersinia enterocolitica* lymphadenitis (lymph nodes of ileum and cecum) is characterized by:

- Non-suppurative epithelioid cell granulomas in germinal centres.
- Suppuration of central granulomas, leading to central micro-abscesses that gradually expand.

- Granulomas composed of epithelioid histiocytes with dispersed, miniature lymphocytes and plasmacytoid monocytes.
- Absence of giant cell reactions and MBL effusion, distinguishing it from granulomas seen in cat scratch disease or lymphogranuloma venereum.

On the other hand, *Yersinia pseudotuberculosis* infection includes:

- Intense, neutrophilic infiltrates
- Small granulomas with disseminated micro-abscesses
- Central suppuration surrounded by histiocytes (suppurative granulomas), resembling epithelioid aggregates seen in cat scratch disease [1].

IV. Lymphogranuloma Venereum Lymphadenitis

Lymphogranuloma venereum (LGV) is a sexually transmitted disease caused by *Chlamydia trachomatis*, a Gram-negative bacterium. It is generally characterized by a small (2-3 mm), painless genital vesicle or ulcer that spontaneously heals within a short period. This is followed by prominent inguinal lymph node enlargement.

Histologically, in the early stages, LGV lymphadenitis presents with a small necrotic locus with neutrophil infiltration, which subsequently progresses to extensive necrotic foci. These necrotic areas fuse to form stellate micro-abscesses that may coalesce and create a cutaneous sinus tract [1].

B. Non Suppurative

I. BCG Lymphadenitis (BCG-Histiocytosis)

According to World Health Organization (WHO) recommendations, the Bacillus Calmette- Guérin (BCG) vaccination with live attenuated strains is generally safe and effective, particularly in preventing severe forms of tuberculosis (TB), such as childhood TB meningitis and miliary TB disease. It also provides protection against leprosy [36].

The vaccine contains an attenuated strain of *Mycobacterium bovis* which, despite being the weakest strain globally, retains antigenic activity. After intradermal injection, the organism multiplies at the inoculation site and spreads to regional lymph nodes and systemic organs within hours. As a result, pathological reactions following BCG vaccination, pathological reactions occur at both the inoculation site and regional lymph nodes (mainly axillary and cervical), where subclinical lymphadenitis is common and often resolves spontaneously [37, 5]. Although disseminated BCG infection (BCGosis) is a rare complication, occurring in 0.06 to 1.56 cases per million vaccinations, it is almost exclusively seen in immunocompromised patients (congenital or acquired). Regional disease (BCGitis) may also occur [37,38]. A study by Wang, Jing et al in Shanghai, China reported 56 cases of adverse events following immunization after BCG vaccination from 2010 to 2019, with 51 cases (91.07%) being BCG lymphadenitis. The overall incidence was 173 per 1,000,000 doses [39].

BCG lymphadenopathy is generally smaller than tuberculous lymphadenopathy. Early histological findings include follicular hyperplasia and sinus histiocytosis. Later, epithelioid granulomas without necrosis appear, progressing to granulomas with central coagulation necrosis. Langhans giant cells are rare [5].

II. Tuberculous and Non-Tuberculous Mycobacteria Lymphadenitis

Mycobacteria are the most common etiologic agents of necrotizing granulomas worldwide. Their clinical and radiographic presentation may resemble malignancy or other infections, but they exhibit distinct histologic features.

Mycobacterium tuberculosis (MTB) is an acid-fast, obligatory aerobe that proliferates within histiocytes. Inhalation of the bacillus induces a granulomatous response in the lungs, leading to a rim of histiocytes and lymphocytes around a necrotic center (Ghon focus). The primary lesion spreads to regional lymph nodes eventually undergoing latency, fibrosis and calcification (Ghon complex). In cases of immune suppression, reactivation may lead to secondary disease with localized cavitation or miliary tuberculosis [3].

Patients with MTB infection typically present with progressively worsening symptoms over weeks to months, including cough, weight loss, fever, night sweats and fatigue, symptoms that may all overlap with sarcoidosis. Radiographic findings of primary TB include hilar and mediastinal lymphadenopathy, pleural effusion, and solitary pulmonary nodules. Reactivation TB often shows focal parenchymal opacities, cavitation, pleural involvement, and endobronchial spread, findings that can also be seen with sarcoidosis complicating diagnosis [10].

Histologically, MTB lymphadenitis varies from small epithelioid granulomas resembling sarcoid granulomas, to large caseating necrotic aggregates surrounded by Langhans giant cells, epithelioid cells, and mature lymphocytes [1]. However, MTB lymphadenitis may

sometimes present with non-caseating granulomas, while sarcoidosis can exhibit necrotic features in up to one-third of cases [10]. Diagnosis requires confirmation via special stains (Ziehl-Neelsen stain), culture, or polymerase chain reaction (PCR).

Non-tuberculous mycobacteria (NTM) include *Mycobacterium kansasii*, M. *marinum, M. gordonae, M. scrofulaceum* and *Mycobacterium avium-intracellulare*. These pathogens infect both immunocompetent and immunocompromised individuals, resulting in variable clinical presentations. Pulmonary disease is the most common manifestation, but NTM infections may also involve the skin, bones, soft tissues and lymph nodes (typically non-tender lymphadenopathy) [40]. Histologically, NTM lymphadenitis features well-formed granulomas with or without caseous necrosis and histiocytes laden with acid-fast bacilli.[3]However the morphologic differences between MTB and NTM infections on Ziehl-Neelsen staining are unreliable. Culture or molecular assays are required for definitive identification [10].

III. Toxoplasma Lymphadenitis

Toxoplasmosis is a parasitic infection caused by *Toxoplasma gondii*. Humans, as intermediate hosts, acquire infection through transplacental transmission, ingestion of undercooked meat, contaminated water, or contact with infected cats and their feces. In immunocompetent individuals, toxoplasmosis is often asymptomatic or presents with symptoms resembling infectious mononucleosis. However, in fetuses and immunocompromised patients (e.g., those with AIDS, hematologic malignancies or on immunosuppressive therapy) it may cause myocarditis, pneumonitis, chorioretinitis, encephalitis or even death [5].

Lymphadenopathy is typically localized, firm, and moderately enlarged, most commonly affecting the posterior cervical lymph nodes. Three characteristic histological features include florid follicular hyperplasia, small epithelioid granulomas (mainly at the follicular periphery) and dilated marginal and cortical sinuses with MBLs. Necrosis and Langhass giants cells are rare [1].

IV. Leprosy

Leprosy (Hansen's disease) is a chronic cutaneous infection caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis* [41]. It progresses through multiple stages from tuberculoid (high resistance, few skin lesions) to lepromatous leprosy (low resistance, multiple skin and visceral lesions) [3].

Clinically, leprosy presents with thickened cutaneous nerves and maculoanesthetic skin patches [2]. While lymphadenopathy is usually non-suppurative, acute necrotizing suppurative lymphadenitis has been reported in rare cases [41].

V. Syphilis

Syphilis is a sexually transmitted disease caused by the Gram-negative spirochete *Treponema pallidum*. Known as "the great imitator" it can present with a wide range of clinical manifestations. Granulomatous inflammation occurs primarily in tertiary syphilis and, rarely, in the secondary syphilis [42].

VI. Fungal Infections

Fungal infections may lead to granulomatous lesions in lymph nodes, which can be either suppurative or non-suppurative [30]. Coccidioidomycosis, also known as Valley fever, is caused by *Coccidioides immitis* and *Coccidioides posadasii*, both of which are found in the soil of endemic regions such as southwestern United States. Transmission to humans occurs through inhalation or direct inoculation [3].

The most common presentations include asymptomatic infection or pulmonary coccidiodomycosis, which manifests with cough, fever, and erythema nodosum [2]. In immunocompetent patients, the disease is typically self-limiting, but in immunocompromised individuals, disseminated disease may occur [3]. When endospores form, they trigger a granulomatous, T-cell mediated host response. Recruited histiocytes phagocytize the endospores, which subsequently migrate into regional lymphatics, leading to lymphangitis or lymphadenitis. When fungal stains reveal small yeast forms, the differential diagnosis should include *Histoplasma capsulatum* and *Cryptococcus spp.*, both of which can also be associated with necrotizing granulomas [3]. In immunocompetent patients, *Histoplasma* infections in the lungs cause epithelioid cell granulomas with coagulative necrosis. However, in immunosuppressed individuals with fulminant disease, granulomas may be absent [2]. Histoplasmosis may lead to extensive necrosis of the lymph nodes, accompanied by prominent and diffuse hyperplasia of sinus histiocytes [1]. Fungal infections may also be opportunistic infections such as cryptococcosis, aspergillosis, mucormycosis and candidiasis, all of which can involve lymph nodes [1].

VII. Brucellosis

Brucellosis, a zoonotic infection, is caused by *Brucella melitensis* (most common), *B. abortus, B. canis*and *B. suis*. It is primarily transmitted through unpasteurized dairy products. Symptoms include fever, night sweats, chills, headaches, joint pain and lymphadenopathy [43]. Histologically, affected lymph nodes exhibit follicular hyperplasia, epithelioid cell aggregates and non-caseating granulomas [1].

CONCLUSIONS

In conclusion, granulomatous lymphadenopathy is a non-specific finding that can be seen in a variety of conditions, including infections, autoimmune diseases, malignancies or drug reactions. Although its presence alone is not diagnostic, it serves as an important clue for investigating potential causes. Its clinical value lies in prompting further workup, such as microbiological testing, imaging, and biopsy, to find the underlying condition and give the appropriate therapy. A thorough understanding of the patient's history, clinical presentation, and associated findings is crucial for making an accurate diagnosis and guiding appropriate management.

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Corresponding author:

Dimitrios Efthymiou, MD, PhDc
Department of Internal Medicine, University Hospital of Patras, 26504 Patras, Greece
Tel.: +30 2613603582, E-mail: efthdim2@gmail.com

Intravenous Contrast Agents: Risk of Renal Complications

Marios Papasotiriou[1], Adamantia Bratsiakou[1], Panagiotis Kitrou[2], Themistoklis Paraskevas[1], Evangelos Papachristou[1]

Abstract

The need for intravenous contrast-enhanced imaging, either in the acute or outpatient setting, is steadily increasing over the last years. A common concern for both clinicians and radiologists is the probability of the associated renal complications. In this review we present contemporary data on the safety and risk of development of acute kidney injury (AKI) after the administration of iodinated contrast agents and the development of nephrogenic systemic fibrosis (NSF) after gadolinium-based contrast media exposure (GBCM). Although the risk of AKI after iodinated contrast enhanced imaging is higher in patients with established chronic kidney disease and decreased kidney function, the direct link between these agents and induced AKI is missing as there are no well designed randomized controlled trials to support causal relationship. However, in patients with an estimated glomerular filtration rate of less than 30 ml/min/1.73m^2, prophylaxis should be applied with intravenous hydration with normal saline before performing the exam and cessation of metformin and other possible nephrotoxic drugs. Concerning GBCM exposure and NSF, current data and guidelines support that the risk for NSF development is minimal (if any) with modern GBCMs even in patients with end stage kidney disease.

Key words: *Contrast associated AKI; contrast induced AKI; nephrogenic systemic fibrosis*

INTRODUCTION

One of the most debilitating adverse effects reported after intravenous radiocontrast administration is acute kidney injury (AKI) of various stages and severity (Table 1) [1]. However, several recent observational but not randomized control studies have shown that such an association between contrast administration and AKI does not exist in the current era of modern agents and doses [2]. This notion though has several potential biases based on the baseline characteristics of patients involved, mainly concerning differences on the risk for AKI or even the appropriately timed repeat creatinine measurements. In any case, and despite several studies showing no evidence of connection between radiocontrast administration and AKI, many clinicians may still express concern over contrast exposure in patients with reduced kidney function or even avoid diagnostic imaging due to fear of AKI especially in the acute setting [3]. Thus, in this review we will examine the evidence from the most important studies on the risk of renal complications after the administration of intravenous contrast agents.

Contrast-associated acute kidney injury (CA-AKI) and contrast-induced acute kidney injury

An AKI that occurs within 48 hours of contrast administration is referred to as contrast-associated (CA-AKI). Whereas an AKI that can be causally linked to contrast

[1]Department of Nephrology and Kidney Transplantation, University Hospital of Patras, Patras, Greece
[2]Department of Interventional Radiology, University Hospital of Patras, Patras, Greece
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Table 1. *AKI stages according to baseline serum creatinine values and urine output.*

Stage	Serum Creatinine	Urine output
1	1.5-1.9 times baseline or ≥ 0.3 mg/dl increase	< 0.5 ml/kg/h for 6-12 hours
2	2-2.9 times baseline	< 0.5 ml/kg/h for ≥ 6-12 hours
3	3 times baseline or increase in serum creatinine ≥ 4 mg/dl or initiation of renal replacement therapy	< 0.3 ml/kg/h for ≥ 24 hours or anuria for ≥ 12 hours

administration is referred to as contrast-induced acute kidney injury (CI-AKI). CI-AKI is a subset of CA-AKI and suggests a causal relationship between intravenous contrast administration and the development of AKI. Only studies with a well-matched control group can demonstrate a possible causal relationship of iodinated contrast administration with the development of acute kidney injury [4]. While there is much evidence for the existence of CA-AKI, studies related to CI-AKI are only few.

Presumed pathogenesis of contrast induced AKI

Following intravascular administration, iodinated contrast agents cause immediate and short-term renal vasodilation which is very soon followed by vasoconstriction [5]. In some animal models, the intravascular administration of iodinated contrast results in decreased renal blood flow and a reduction in the partial pressure of oxygen of the outer renal medulla [6]. This adverse hemodynamic effect of contrast is also observed in studies of healthy human subjects [7]. Moreover, iodine contrast drugs can induce osmotic diuresis which in turn promote tubular flow, O2 consumption and enhance tubular epithelial cell injury [8].

contrast-associated AKI

The risk of CA-AKI (AKI of any etiology after iodinated contrast administration) increases with each increase in chronic kidney disease (CKD) stage. Using the KDIGO stage I based on serum creatinine criteria, the risk of CA-AKI is approximately 5% greater for estimated glomerular filtration rate (eGFR) of 60– 90 mL/min/1.73 m^2, 10% for eGFR 45–59 mL/ min/1.73 m^2, 15% for eGFR 30–44 mL/ min/1.73 m^2, and 30% for eGFR less than 30 mL/min/1.73 m^2 [9]. This risk is much higher than the risk of CI-AKI because it includes any AKI that coincides with contrast media administration [4]. Multiple patient-related risk factors have been associated with CA-AKI. The primary risk factor is low eGFR. Some studies find diabetes mellitus to be an additional risk of CA-AKI. Additional risk factors include administration of nephrotoxic agents, hypotension and hypovolemia, albuminuria, and reduced renal perfusion (e.g., congestive heart failure) [10].

Effect of contrast medium osmolality

The initial contrast media used in clinical practice were 'high osmolal' with osmolalities much greater than blood (i.e., 1500–2000 mOsm/kg). Following the introduction of 'low-osmolal' contrast media (osmolality ~ 600–850 mOsm/kg), clinical trials and meta-analyses demonstrated lower risk for CA-AKI with these agents compared with 'high-osmolal' media [11]. Despite their name, low-osmotic contrast media (LOCM) are hyperosmotic (approximately 600 mOsm/kg) relative to both isoosmotic (IOCM) (approximately 290 mOsm/kg) and blood (approximately 290 mOsm/kg). Nevertheless, the chemical structure of IOCMs makes them more viscous than LOCMs and most currently used iodinated contrast media are classified as LOCMs. There are no clinically confirmed differences in the risk of CA-AKI between LOCM and IOCM contrast media. Indirect evidence suggests that iohexol, which is a LOCM, may have a higher risk compared with other LOCMs, but this potential risk difference has not been confirmed [12].

Contrast Induced AKI

In general, the risk of CI-AKI is lower than the risk of CA-AKI, but the risk in those with established severe kidney disease (either high grade CKD or AKI) is not known. Some observational studies have shown no evidence of CI-AKI, irrespective of CKD stage, while others have found evidence of CI-AKI only in patients with severely reduced kidney function [13, 14]. In such studies, the risk of CI-AKI has been estimated to be almost 0% for eGFR greater than or equal to 45, 0%–2% for eGFR 30–44, and 0%– 17% for eGFR less than 30 mL/min/1.73 m^2 [14].

In a study of 12,508 patients the incidence of AKI increased significantly with decreasing baseline eGFR. However, this incidence was not significantly different between the contrast-enhanced and non-contrast-enhanced groups for any eGFR subgroup [9]. Further-

more, a meta-analysis by McDonald and colleagues that included 13 studies with a total of 25,950 patients demonstrated that the risk of AKI following procedures with intravascular contrast administration was similar to the risk following procedures that did not utilize contrast [15]. In a study of 611 patients in total, with a median age of 65 years and a serum creatinine level on the day of computed tomography of 1.13 mg/dl for the non-contrast group and 0.87mg/dl for the contrast-enhanced group, the adjusted odds ratio for developing AKI for the patients who received intravenous contrast media (ICM) was 1.03 (95% CI 0.64–1.66, p=0.90). No significant association was found between ICM and increased plasma creatinine at long-term follow-up [16]. Another cohort study included all emergency department patients aged 18 years and older who underwent a D-dimer test. There was no association of iodinated contrast media administration with eGFR up to 6 months later. Similarly, there was no evidence of an association with the need for renal replacement therapy and the occurrence of AKI. Subgroup analyses showed a possibly higher risk among patients with diabetes [17]. Thus, although no randomized controlled trial has been conducted, evidence suggests that ICMs contribute little, if any, to the occurrence of AKI [18].

Prophylaxis

Overall, patients with CKD stage 4 or 5 have a relative, but not absolute, contraindication to receive iodinated contrast media. If contrast media is required for a life-threatening diagnosis, it should not be withheld based on kidney function. If a decision is made to administer iodinated contrast media, then prophylactic normal saline administration is indicated if there are no contraindications [4]. Due to the lack of proven benefits, risks, and costs, acute dialysis should not be performed or the dialysis schedule changed solely on the basis of iodinated contrast media administration, regardless of residual renal function [4]. Prophylaxis is indicated for patients who have AKI or an eGFR less than 30 mL/min/1.73 m^2 and are not on chronic dialysis. The risks of prophylaxis, especially in hypervolemic patients or those with congestive heart failure should be considered before initiating prophylactic normal saline administration. Prophylaxis is not indicated for the general population or patients with a stable eGFR ≥ 30 mL/min/1.73 m^2 [4].

If an iodinated contrast imaging procedure is urgently indicated and there is insufficient time for prophylaxis, then post-examination prophylaxis can be considered. For prophylaxis, hydration with isotonic saline (0.9% N/S) is the preferred method as other agents such as acetylcysteine or sodium bicarbonate have shown no benefit [19]. Typical N/S 0.9% regimens are initiated 1 hour before and continued 3-12 hours after contrast administration, with doses ranging from fixed (e.g., 500 mL before and after) to weight-based volumes (1-3 mL/kg per hour) but ideal volume or rates of administration are not established. Longer regimens (approximately 12 hours) have been shown to reduce the risk of CA-AKI compared with shorter regimens. Oral hydration has not been well studied [10]. In patients with AKI or eGFR ≤ 30 mL/min/1.73 m^2, potentially nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, antibiotics (aminoglycosides and amphotericin) and chemotherapeutics (platinum) may need to be discontinued for 24 to 48 hours before and 48 hours after exposure [20]. Metformin is another agent that is appropriate to stop before contrast enhanced CT and discontinuation should be maintained for at least 48 hours in this group of patients [21]. It is unknown whether renin-angiotensin-aldosterone system (RAASi) inhibitors should be maintained. Given the lack of strong evidence that continued RAASi is beneficial, consideration should be given to discontinuing RAASi in patients at risk for at least 48 hours before elective contrast-enhanced CT for preventing hyperkalemia and hypotension should AKI develop [21].

Correlation between administration of gadolinium-based contrast media (GBCM) and nephrological complications

The frequency of magnetic resonance imaging (MRI) examinations with the administration of a paramagnetic contrast media has increased significantly in the last decade and is predicted to increase further [22]. In the United States, GBCMs are used in 30% to 45% of the approximately 40 million MRI procedures performed each year [23]. As more patients undergoing these tests are older and suffer from multiple comorbidities, including acute or chronic kidney dysfunction, it is imperative to investigate the possibility of additional burden on kidney function from the administration of the paramagnetic substance or the occurrence of another related nephrological complication. Clarifying the presence of such complications is of particular importance as it is not uncommon to delay or even refuse to perform tests with the administration of a paramagnetic substance in cases of patients with pre-existing chronic kidney

disease and reduced glomerular filtration rate [24].

Gadolinium has been used in most intravenous MRI contrast agents because it is highly paramagnetic, allowing the distinction between normal and abnormal tissues in humans. However, "free" gadolinium exhibits multiple toxicities (mainly cytotoxicity) due to its insolubility [5]. In order to minimize toxicity, gadolinium is chelated to organic ligands, which confer more favorable pharmacological and toxicological properties. Most GBCMs are distributed primarily in the extracellular fluid, exhibit little protein binding, and are excreted primarily in the urine via glomerular filtration. Finally, GBCMs are classified as linear or macrocyclic, based on the molecular structure of the organic ligand, and as nonionic or ionic, based on their net charge in solution (Table 2) [25].

Gadolinium and nephrotoxicity

Gadolinium-based contrast media (GBCM) are in general considered non-nephrotoxic. Nevertheless, at doses considerably higher than the approved dose, GBCM may be nephrotoxic as demonstrated in patients and in experimental settings [26, 27]. Very high doses of GBCM have been associated with cases of AKI, but there are no controlled clinical studies demonstrating a clinically significant nephrotoxic risk at on-label doses [26, 28]. Thus, clinicians should consider that on-label dosing of intravenous group II or group III GBCM does not increase the risk of AKI, and no special precautions are indicated for kidney function safety (Table 2). In general, only the approved GBCM dose (0.1 mmol/kg) should be administered during a single imaging session [29]. Moreover, there are no indications that patients receiving other nephrotoxic agents are at increased risk for AKI after an MRI with GBCM administration and such examinations can be performed as scheduled. Finally, MRIs with GBCMs can be performed irrespective of the timing of additional iodinated contrast CTs without increased risk for AKI [30].

Nephrogenic systemic fibrosis (NSF) and GBCM Exposure

NSF is a potentially fatal systemic fibrotic condition that occurs almost exclusively in patients with AKI or severe CKD (eGFR < 30 mL/min/1.73 m^2). Skin and subcutaneous abnormalities (e.g., skin thickening, pruritus, hyperpigmentation), as well as ocular findings (sclerotic plaques) are common, but NSF can also cause visceral fibrosis (e.g., lung, esophagus, and heart) [31]. NSF is characterized by signs of cutaneous edema and erythema in the extremities that may sometimes progress to thickened, woody, and contracted skin. The condition has been associated with the use of linear GBCMs in patients with advanced CKD and rarely develops (if at all) after the use of macrocyclic GBCMs. In recent years, the incidence of NSF has decreased or disappeared [29].

The link between GBCM and NSF was first identified in 2006 and has since been confirmed in numerous studies [32, 33]. Patients at greatest risk for NSF include those on renal replacement therapy, those with AKI, and those in stages 4 or 5 CKD with exposure to group I GBCMs, especially if repeated doses of group I GBCMs are administered or at higher than recommended doses [30].

The risk of developing NSF differs between the different groups of GBCM (Table 2). Most NSF cases have been associated with Group I GBCMs, however, this

Table 2. *Classification of GBCMs related to association with Nephrogenic Systemic Fibrosis.*

Substance	Structure	American College of Radiology Group
Gadodiamide	Linearnonionic	I
Gadoversetamide	Linearnonionic	I
Gadopentetatedimeglumine	Linearionic	I
Gadobenatedimeglumine	Linearionic	II
Gadoteridol	Macrocyclic non ionic	II
Gadobutrol	Macrocyclic non ionic	II
Gadoterateme glumine	Macrocyclic ionic	II
Gadoterateme glumine	Macrocyclic ionic	II
Gadoxetatedi sodium	Linear ionic	III

group of contrast media is by now mostly not used at all. For Group II, only a few (if any) cases of NSF have been reported [34] and for Group III GBCMs again only a few (if any) cases have been reported [35]. In a recent meta-analysis of 16 studies, including 4931 patients with CKD stage 4 or 5 who were given a Group II GBCM and followed for up to 72 months, no NSF was reported [34]. In a meta-analysis of observational studies, all patients with NSF were reported to have renal dysfunction with a higher risk of NSF for GFR < 15 ml/min (i.e., stage 5 CKD). Eighty percent (296 of 370) of patients with NSF were on dialysis, suggesting that this is an important risk factor. For 57 patients with NSF who were probably not on dialysis, GFR was reported to range from 0 to 40 ml/min, with a mean of 15 ml/min, but most importantly, the majority of these patients (88%) had received a higher than standard dose and in some cases GBCMs were administered intra-arterially [36]. In general, only the approved dose of GBCM should be administered but the use of a lower dose for NSF prevention is not supported and may compromise image quality [34].

Excretion of GBCAs is dependent on kidney function and in patients with normal GFR, GBCMs half-life is approximately 1.5 hours, with the majority excreted within 24 hours. Thus, in patients with established CKD or AKI, the half-life of GBCMs is prolonged according to CKD or AKI stage with a span of more than 24 hours in severely diminished GFR [37, 38]. Accordingly, hemodialysis removes sufficiently GBCAs with ~70% clearance after 1 session [30], but such intervention offers no proven reduction in the risk of NSF development [39]. Furthermore, in patients with end stage kidney disease on maintenance hemodialysis, GBCMs should better be administered before a scheduled dialysis session but otherwise sessions should be performed on the regularly scheduled basis [29]. Overall, the risk of NSF is extremely low for group II GBCMs even in patients with diminished kidney function and based on these data, many societies have issued recommendations to liberalize the administration of group II GBCMs [40, 41].

CONCLUSION

Modern iodinated contrast agents [LOCM, IOSC) are minimally nephrotoxic in patients with eGFR > 30 ml/min/1.73m^2. However, in patients with compromised renal function (AKI or eGFR < 30 ml/min/1.73m^2), measures should be taken to reduce potential nephrotoxicity, including intravenous hydration with 0.9% N/S and discontinuation of nephrotoxic agents. Well-designed prospective RCTs in patients with similar clinical characteristics and morbidities are necessary to clarify the type and degree of potential nephrotoxicity of iodinated contrast agents, especially in patients with impaired kidney function. Modern paramagnetic contrast agents at the recommended dose are not nephrotoxic and are rarely (if at all) associated with the occurrence of NSF.

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Corresponding author:

Marios Papasotiriou, MD, PhD
Department of Nephrology and Kidney Transplantation,
University Hospital of Patras, Patras, Greece
Tel/Fax: +30 2613 603 372
E-mail: mpapasotiriou@yahoo.com, mpapasotir@upatras.gr

Investigation of Elevated Aminotransferases

Stamatia Tsoupra

Abstract

Elevated aminotransferase levels, specifically alanine transaminase (ALT) and aspartate transaminase (AST), are common findings in clinical practice, often indicating hepatocellular injury. These elevations can result from a variety of causes, including metabolic dysfunction-associated steatotic liver disease (MASLD), alcoholic liver disease (ALD), viral hepatitis, medication-induced liver injury (DILI), and metabolic disorders, such as hemochromatosis and Wilson's disease. The evaluation of elevated aminotransferases should begin with a thorough history and physical examination to identify potential etiologies. Subsequent investigations may include serologic tests for viral hepatitis, assessments for metabolic and genetic liver diseases, and imaging studies to evaluate liver morphology. In cases where initial evaluations are inconclusive, a liver biopsy may be warranted to obtain a definitive diagnosis. Management strategies are directed at the underlying cause of the enzyme elevation. For instance, lifestyle modifications, including weight loss and dietary changes, are recommended for patients with MASLD. Regular monitoring of liver enzymes is essential to assess disease progression and response to therapy. In summary, elevated aminotransferases are frequently encountered and can signify a spectrum of liver disorders and polysystemic diseases. A systematic approach to evaluation and management is crucial for accurate diagnosis and effective treatment.

Key words: *Aminotransferases; elevated liver enzymes; hepatocellular injury*

INTRODUCTION

The evaluation of abnormal liver tests is a common concern in clinical practice, given that liver enzymes are frequently included in routine blood panels. As such, elevated liver enzymes, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are frequently detected even in asymptomatic patients. Although the term "liver function tests" (LFTs) is widely used, it is somewhat misleading. Many of the tests used to assess liver health, including ALT and AST, are not direct measures of liver function. For example, ALT and AST are primarily markers of hepatocyte injury, rather than direct indicators of liver function such as the liver's ability to synthesize proteins or produce bile. Therefore, an isolated elevation of these enzymes does not necessarily imply liver failure, but instead, liver injury or damage, which can arise from a variety of causes [1]. It is crucial to interpret these markers within the broader context of clinical symptoms, history, and other laboratory findings.

Understanding the underlying causes of elevated aminotransferases is essential for proper patient management. Hepatic causes of elevated aminotransferases are diverse, including viral hepatitis (such as hepatitis A, B, or C), alcoholic liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and autoimmune conditions like autoimmune hepatitis. Furthermore, genetic disorders such as Wilson's disease and hemochromatosis can also present with elevated liver enzymes. In addition to these hepatic causes, extrahepatic conditions must also be considered. These include muscle injuries like rhabdomyolysis, hemolysis, thyroid disorders, and metabolic conditions such as celiac disease or adrenal insufficiency. It is important for clinicians to approach these cases with a systematic diagnostic process to distinguish between hepatic and

Department of Internal Medicine, University General Hospital of Patras, Patras, Greece

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extrahepatic causes, as treatment and management strategies will vary widely depending on the etiology.

The diagnostic approach to elevated aminotransferases involves several steps. A thorough medical history is critical in identifying potential causes, including any exposure to hepatotoxins such as alcohol or medications, as well as risk factors for viral hepatitis. For example, intravenous drug use, blood transfusions, or travel to regions endemic for hepatitis B or C can increase the likelihood of viral hepatitis. A comprehensive physical examination may also reveal clues to the cause of liver dysfunction, such as signs of chronic liver disease like spider nevi, ascites, or hepatomegaly. Laboratory tests, including ALT, AST, bilirubin, and alkaline phosphatase, provide valuable information, and imaging techniques like ultrasound or CT/ MRI scans may be required to assess liver morphology and the extent of fibrosis. In cases where the diagnosis remains unclear, liver biopsy can be a valuable tool, although it is typically reserved for more advanced cases or when non-invasive tests are inconclusive.

The management of elevated aminotransferases depends on the underlying cause and ranges from lifestyle changes to pharmacological intervention [2]. For instance, viral hepatitis may require antiviral therapy, while autoimmune conditions could be managed with immunosuppressants. MASLD is increasingly recognized as a significant cause of elevated liver enzymes. These patients often benefit from weight loss and control of metabolic risk factors. In some cases, such as with Wilson's disease or hemochromatosis, chelation therapy may be necessary. Regardless of the underlying cause, regular monitoring of liver function is recommended, especially for chronic conditions, to prevent progression to more severe liver damage, such as cirrhosis or liver failure. Thus, a structured, stepwise diagnostic and management approach is essential in optimizing patient outcomes, ensuring timely intervention, and preventing irreversible liver damage.

CAUSES OF ELEVATED AMINOTRANSFERASES

Hepatic Causes of Elevated Aminotransferases

Viral Hepatitis (HAV, HBV, HCV, HDV, HEV)

Viral hepatitis is one of the most common causes of elevated aminotransferases, with Hepatitis A (HAV), B (HBV), and C (HCV) being the main culprits. These viruses cause inflammation of the liver, leading to hepatocellular injury, which results in the release of ALT and AST into the bloodstream. Hepatitis D virus requires the presence of Hepatitis B virus (HBV) to replicate. It can be transmitted through contact with infected blood, sexual contact, and from mother to child during childbirth. Hepatitis A and E, typically transmitted via the fecal-oral route, often causes acute, self-limiting disease. In contrast, Hepatitis B and especially C can lead to chronic infections that may progress to cirrhosis and hepatocellular carcinoma (HCC) if not properly managed. Chronic hepatitis B and C infections result in persistently elevated aminotransferases and can be detected by measuring viral load and liver function tests [3,4].

Metabolic dysfunction-associated steatotic liver disease (MASLD)

MASLD, once called nonalcoholic fatty liver disease (NAFLD), is closely associated with metabolic syndrome and obesity, and it has emerged as one of the most prevalent causes of liver enzyme elevation worldwide. MASLD refers to the accumulation of fat in liver cells without excessive alcohol intake, and includes conditions ranging from simple fatty liver to metabolic dysfunction-associated steatohepatitis (MASH), which can progress to cirrhosis and HCC. Elevated aminotransferases, especially ALT, are commonly observed in MASLD, with ALT often outpacing AST. The pathogenesis of this condition is thought to involve insulin resistance, oxidative stress, and inflammation, which promote fat accumulation and liver injury. Studies have indicated that the prevalence of MASLD correlates with the rising global incidence of obesity and type 2 diabetes mellitus [5,6]. Non-invasive markers such as the NAFLD fibrosis score can help in assessing disease progression.

Alcoholic Liver Disease (ALD)

Alcoholic liver disease (ALD) is a leading cause of liver dysfunction and elevated aminotransferases, especially in individuals with heavy and prolonged alcohol consumption. The liver's primary role in alcohol metabolism involves the enzyme alcohol dehydrogenase, which breaks down ethanol to acetaldehyde, a toxic substance that can lead to liver inflammation and damage. In the early stages, ALD may cause elevated ALT and AST levels, with a characteristic AST-to-ALT ratio greater than 2:1. Chronic ALD can lead to fatty liver, alcoholic hepatitis, and eventually cirrhosis, with substantial increases in liver enzymes [7]. Additionally, the development of alcoholic liver disease is influenced by genetic and environmental factors, highlighting the complexity of its pathogenesis.

Drug-Induced Liver Injury (DILI)

Drug-induced liver injury (DILI) is a well-known cause of elevated aminotransferases, and it can result from a wide variety of substances, pharmaceutical agents, both over the counter and prescription medications. Drugs such as acetaminophen, statins, and antibiotics are frequently associated with liver toxicity, leading to hepatocellular damage and enzyme elevation. DILI can present as acute or chronic liver injury, with elevated ALT and AST levels being one of the first signs. Acetaminophen overdose is particularly notorious for causing acute liver failure and dramatically raising aminotransferase levels. The mechanism of drug-induced hepatotoxicity is complex, involving both dose-dependent and immune-mediated pathways. Genetic factors, including polymorphisms in drug-metabolizing enzymes, also play a critical role in susceptibility to DILI [8]. The management of DILI typically requires discontinuing the offending drug and providing supportive care, though in severe cases, liver transplantation may be necessary.

Extrahepatic Causes of Elevated Aminotransferases

Muscle Injury (Myositis, Rhabdomyolysis)

Muscle injury, particularly conditions like myositis and rhabdomyolysis, can lead to elevated aminotransferase levels, especially AST, due to the release of these enzymes from damaged muscle cells. Rhabdomyolysis, in which skeletal muscle tissue breaks down and releases intracellular contents into the bloodstream, can cause a dramatic increase in aminotransferases. This condition is often triggered by trauma, prolonged immobilization, strenuous physical activity, or the use of certain medications, including statins. Elevated AST in this context may be disproportionate to ALT levels, as AST is also present in muscle tissue. Myositis, an inflammatory condition of the muscles, can also elevate aminotransferases but typically in lower concentrations compared to rhabdomyolysis. The increased release of enzymes, such as AST and creatine kinase (CK), can indicate the severity of muscle damage and aid in diagnosing these conditions [9,10]. Prompt recognition and management of the underlying cause, including hydration and cessation of any contributing medications, are key to preventing complications such as renal failure, which can occur in severe cases of rhabdomyolysis.

Hemolysis

Hemolysis, the destruction of red blood cells, can also result in elevated aminotransferases, particularly in cases of severe hemolytic anemia. While the primary markers of hemolysis are elevated levels of indirect bilirubin and lactate dehydrogenase (LDH), aminotransferases can be mildly elevated as a secondary effect. The release of AST from red blood cells during hemolysis can contribute to elevated liver enzymes, although the increase is often mild compared to other causes like viral hepatitis or liver disease. Hemolysis may be caused by autoimmune disorders, infections, or certain drugs that target red blood cells. In the setting of hemolytic disease, the liver's role in processing the breakdown products of red blood cells, such as heme, can further complicate enzyme elevation. Monitoring the pattern of aminotransferase elevation in conjunction with other hemolysis markers is essential in distinguishing hemolysis-related increases from liver-specific causes [11]. Treatment includes addressing the underlying cause that caused the hemolysis, such as blood transfusions for the anemia or immunosuppressive therapy in autoimmune conditions.

Thyroid Disorders and Adrenal Insufficiency

Thyroid disorders, including both hypothyroidism and hyperthyroidism, can influence liver enzyme levels and lead to the elevation of aminotransferases. In hypothyroidism, the slowdown of metabolic processes may lead to a reduction in liver blood flow, which can result in mild hepatocellular damage and consequently elevated aminotransferase levels. The enzyme ALT is typically more affected than AST in hypothyroidism. On the other hand, hyperthyroidism, characterized by overproduction of thyroid hormones, can result in increased hepatic metabolism and, in some cases, hepatocellular injury. Both thyroid conditions may also affect lipid metabolism, leading to MASLD and further enzyme elevations. Monitoring thyroid function in patients with unexplained liver enzyme abnormalities is crucial, as proper management of thyroid disorders often leads to normalization of aminotransferase levels [12,13]. Treatment strategies include hormone replacement for hypothyroidism and anti-thyroid medications or radioactive iodine for hyperthyroidism. Similarly, adrenal insufficiency, which results from inadequate cortisol production due to primary adrenal failure or secondary pituitary dysfunction, can also cause elevated aminotransferases. The pathophysiology behind this elevation is not entirely understood, but it may involve impaired metabolic function in the liver due to insufficient cortisol, which plays a role in glucose and fat metabolism. In both conditions, diagnosing the underly-

ing disease and addressing the root cause is crucial for normalizing liver enzyme levels and preventing further complications [14,15].

Celiac Disease

Celiac disease, an autoimmune disorder triggered by the ingestion of gluten in genetically predisposed individuals, is another extrahepatic cause of elevated aminotransferases. Although the primary manifestations of celiac disease are gastrointestinal, liver involvement can occur in up to 50% of patients, often presenting with elevated ALT and AST levels. Liver damage in celiac disease is believed to be immune-mediated, with inflammation and fibrosis contributing to enzyme elevation [15]. Once a gluten-free diet is implemented, liver enzymes often normalize, though some patients may experience persistent mild elevations.

Diagnostic Approach to Elevated Aminotransferases

History & Clinical Examination

The diagnostic approach to elevated aminotransferases begins with a detailed history and clinical examination. A thorough patient history is crucial, as it can provide insights into potential causes of liver enzyme abnormalities. Key factors to explore include medication use, alcohol intake, metabolic risk factors, and family history. Medications, both prescription and over the counter, as well as herbal supplements, are known contributors to DILI, which can cause significant elevations in aminotransferases. Alcohol consumption is a major risk factor for hepatic conditions such as alcoholic liver disease, which typically presents with elevated AST to ALT ratios. Metabolic risk factors, including obesity, diabetes, and hyperlipidemia, are strongly associated with MASLD and MASH. Family history might provide information regarding inherited conditions like hemochromatosis or Wilson's disease, which can lead to chronic liver damage and elevated liver enzymes. Clinicians should look for signs of liver disease such as jaundice, hepatomegaly, and ascites, and physical findings of systemic conditions like thyroid disease or muscle tenderness, which may point to extrahepatic causes of elevated aminotransferases [17,18].

Laboratory Tests

Laboratory testing is essential for further evaluating elevated aminotransferases and identifying the underlying cause. The initial blood tests typically include ALT and AST, bilirubin, alkaline phosphatase, and viral hepatitis serologies. ALT and AST levels are the primary markers of hepatocellular injury, with ALT being more liver-specific and AST being present in other tissues such as muscle. An elevated ALT-to-AST ratio is often seen in liver diseases like MASLD, while a higher AST-to-ALT ratio may suggest alcoholic liver disease or cirrhosis. Bilirubin levels, both total and direct, help assess the liver's ability to excrete waste products and can indicate jaundice. Alkaline phosphatase (ALP) is useful for identifying cholestatic liver diseases, such as primary biliary cirrhosis or gallstone disease. Viral hepatitis serologies, including tests for hepatitis A, B, C, D, E, are necessary to rule out viral infections that are common causes of liver enzyme elevation. Autoimmune markers (e.g., antinuclear antibody [ANA], anti-smooth muscle antibody [SMA]) are essential when autoimmune conditions of the liver, such as autoimmune hepatitis, are suspected. Iron studies, including ferritin and transferrin saturation, can help diagnose conditions like hemochromatosis, a genetic disorder leading to iron overload and liver damage [19,20].

Imaging

Imaging studies play a significant role in the diagnostic evaluation of liver diseases, particularly in assessing hepatic morphology and fibrosis. Ultrasound is the first-line imaging modality due to its non-invasive nature and ability to detect signs of liver disease, such as hepatomegaly, steatosis (fatty liver), and cirrhosis. It can also be used to rule out biliary obstructions, such as gallstones or tumors that might cause secondary liver enzyme elevation. In cases where ultrasound findings are inconclusive or further assessment is needed, more advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are employed. CT scans provide detailed images of liver structure and are useful in detecting liver masses, cysts, or tumors. MRI, especially with the addition of elastography, offers superior visualization of liver tissue and can help assess the degree of liver fibrosis, a critical determinant of liver disease prognosis. These imaging modalities are invaluable for evaluating chronic liver conditions and can help guide decisions about biopsy or other interventions [21,22].

Liver Biopsy

In cases where the diagnosis remains uncertain despite history, clinical examination, laboratory tests, and imaging studies, a liver biopsy is often considered

to obtain a definitive diagnosis. Liver biopsy is the gold standard for assessing the degree of liver damage and fibrosis in conditions like MASLD and autoimmune hepatitis. It involves obtaining a small sample of liver tissue for histopathological examination, which allows for the identification of inflammatory activity, fibrosis, or cirrhosis. Biopsy is particularly valuable in situations where the diagnosis is unclear or when there is a need to assess the stage of liver disease, such as in patients with MASH, where liver damage can range from simple steatosis to advanced cirrhosis. However, because liver biopsy is an invasive procedure with potential risks, it is reserved for cases where the benefits outweigh the risks. Non-invasive methods, such as elastography and serum biomarkers, are increasingly being used as alternatives to biopsy in the evaluation of liver fibrosis [23,24].

Management and Treatment of Elevated Aminotransferases

Management Guided by Underlying Etiology

The management of elevated aminotransferases hinges on identifying and addressing the underlying etiology of the liver injury. Since elevated aminotransferases can arise from a broad spectrum of liver and extrahepatic conditions, treatment strategies vary significantly depending on the cause. For viral hepatitis, antiviral therapy is the cornerstone of management. In contrast, for autoimmune hepatitis, immunosuppressive therapy, including corticosteroids and azathioprine, is used to reduce hepatic inflammation and prevent progression to cirrhosis [25]. For conditions like hemochromatosis and Wilson's disease, treatment involves chelation therapy to remove excess iron or copper from the body, respectively, preventing further liver damage and systemic complications. Understanding the precise cause of liver enzyme elevation allows for tailored interventions aimed at mitigating damage, improving liver function, and reducing the risk of long-term complications.

Antiviral Therapy and Immunosuppressants

For viral causes of elevated aminotransferases, antiviral therapy plays a critical role in preventing liver damage and improving long-term outcomes. In chronic hepatitis B, antiviral agents like tenofovir and entecavir help suppress viral replication, thereby reducing the risk of liver cirrhosis, HCC, and the need for liver transplantation [26]. HCV has a more favorable prognosis with the advent of direct-acting antivirals (DAAs), which target specific steps in the viral lifecycle, offering cure rates exceeding 95% in most patients [27,28]. For patients with autoimmune hepatitis, immunosuppressive therapy is often necessary to prevent further liver damage. Corticosteroids, such as prednisone, and immunosuppressive drugs like azathioprine are commonly used to reduce inflammation and halt the progression to cirrhosis [25]. In some cases, patients who are refractory to conventional immunosuppressive therapy may require alternative treatments such as mycophenolate mofetil or tacrolimus. The choice of therapy in autoimmune hepatitis depends on the severity of liver damage and the response to initial treatment. For patients with Wilson's disease, chelation therapy with agents like penicillamine or trientine is used to remove excess copper from the body, while for hemochromatosis, therapeutic phlebotomy is employed to reduce iron levels and prevent further liver damage [29].

Lifestyle Interventions in Chronic Liver Diseases

For many non-viral and non-autoimmune causes of elevated aminotransferases, lifestyle modifications form the foundation of management. MASLD and its more severe form, MASH, are strongly associated with metabolic syndrome, including obesity, diabetes, and hyperlipidemia. In these cases, weight loss through a combination of diet and physical activity is the primary intervention. Studies have demonstrated that even modest weight loss (5-10% of body weight) can significantly reduce liver fat and inflammation, leading to improved aminotransferase levels and reduced risk of progression to cirrhosis [30]. Patients with MASLD are also encouraged to adopt a Mediterranean-style diet, which is rich in antioxidants and healthy fats and has been shown to improve liver function. In addition to dietary changes, the management of associated metabolic risk factors, such as controlling blood sugar levels in diabetic patients and using statins to manage hyperlipidemia, is crucial to prevent further liver injury and reduce the burden of cardiovascular disease, which is a common comorbidity in these patients [31]. Lifestyle changes, such as smoking cessation and limiting alcohol intake, are also essential in protecting liver health [32].

Regular Monitoring and Follow-up in Chronic Liver Diseases

For patients with chronic liver diseases, regular monitoring and follow-up are essential to assess liver function, track the progression of the disease, and detect

complications early. Monitoring aminotransferase levels, bilirubin, and alkaline phosphatase is crucial in evaluating the response to treatment and detecting any signs of disease progression, such as fibrosis or cirrhosis. Liver function tests should be repeated periodically to assess the effectiveness of lifestyle interventions, antiviral therapy, or immunosuppressive treatment. In addition to laboratory tests, imaging studies such as ultrasound, elastography, or MRI can help monitor the degree of liver fibrosis and assess the risk of cirrhosis or liver cancer. For patients with chronic hepatitis or MASLD, regular screenings for HCC are also recommended, especially for those with advanced liver disease. In patients with cirrhosis, surveillance for esophageal varices and other complications of portal hypertension should be carried out to prevent life-threatening bleeding. The overall goal of regular monitoring is to optimize treatment, prevent complications, and improve the quality of life for patients with chronic liver conditions [33].

DISCUSSION ON ELEVATED AMINOTRANSFERASES AND LIVER DISEASE

Rising Prevalence of MASLD and Metabolic Syndrome

MASLD has become one of the most common causes of elevated aminotransferases, largely due to the rising global prevalence of metabolic syndrome. Metabolic syndrome, a cluster of risk factors that include obesity, hypertension, dyslipidemia, and insulin resistance, is strongly associated with MASLD [34]. In fact, MASLD has now emerged as a major cause of chronic liver disease, affecting a significant portion of the adult population worldwide. The global prevalence of MASLD is estimated to be around 25-30%, and this number is expected to rise due to the increasing incidence of obesity and type 2 diabetes [35]. Elevated aminotransferases, particularly ALT, are often the first indicators of liver dysfunction in patients with metabolic syndrome, as the liver is directly affected by factors such as insulin resistance and the accumulation of fat within hepatocytes. This trend underscores the importance of monitoring liver enzymes in individuals with metabolic risk factors to identify liver abnormalities early, potentially preventing the progression to more severe liver conditions such as MASH or cirrhosis.

Impact of Early Identification on Liver Disease Progression

Early identification of liver disease, especially in patients with metabolic syndrome and MASLD, is crucial to preventing the progression of liver damage to cirrhosis and hepatic failure. Without intervention, MASLD can progress to more severe forms of liver disease, including MASH, cirrhosis, and eventually liver failure or HCC [31]. However, the progression from simple hepatic steatosis (fat accumulation in the liver) to MASH, which is characterized by inflammation and fibrosis, is not inevitable. In many cases, lifestyle modifications such as weight loss, a healthy diet, and exercise can reverse liver damage, especially in the early stages of the disease. Studies have demonstrated that even a modest weight loss of 5-10% can improve liver histology and reduce the risk of fibrosis progression [35]. Moreover, managing associated metabolic conditions such as obesity and diabetes is essential to reducing the burden of liver disease. For patients with metabolic syndrome, managing risk factors through medications and lifestyle changes can lead to substantial improvements in aminotransferase levels and overall liver health. This highlights the importance of early screening and monitoring of liver enzymes, as timely interventions can prevent irreversible liver damage.

Non-invasive Biomarkers for Liver Health Assessment

One of the key challenges in the management of liver diseases is the lack of reliable, non-invasive biomarkers to assess liver health, particularly for the early stages of the disease. Currently, liver biopsy remains the gold standard for diagnosing the severity of liver damage, such as fibrosis or cirrhosis. However, this procedure is invasive, expensive, and carries risks such as abdominal pain and hemorrhage, which has prompted a growing interest in non-invasive diagnostic methods. Several non-invasive biomarkers have been proposed, including serum markers, imaging techniques such as elastography, and novel biomarkers like the Fibrosis-4 (FIB-4) index or the NAFLD fibrosis score (NFS) [33]. These tests have been shown to correlate well with liver fibrosis and can be used to monitor disease progression and response to treatment. Additionally, imaging techniques like ultrasound and magnetic resonance elastography (MRE) provide valuable insights into liver stiffness, which is indicative of fibrosis [34]. However, despite the progress in developing non-invasive biomarkers, there is still a need for further research to refine these tools and validate their use in clinical practice. The development of highly sensitive and specific biomarkers that can reli-

ably assess liver health and predict disease progression would significantly aid early diagnosis, reduce reliance on invasive procedures, and help tailor individualized treatments.

The Need for Continued Research and Advances in Diagnostics

Although there have been significant strides in understanding the pathophysiology of MASLD and other liver diseases, continued research is essential to improve diagnostics and treatment options. As the prevalence of metabolic syndrome and MASLD continues to rise globally, it is increasingly important to focus on refining non-invasive methods for liver health assessment. For example, while liver function tests like aminotransferases are useful for detecting liver injury, they lack specificity for detecting early stages of liver disease. Novel biomarkers that can detect fatty liver, liver inflammation, and early fibrosis without the need for a biopsy could significantly improve patient outcomes by enabling earlier intervention. Moreover, research into the molecular mechanisms underlying MASLD and its progression to MASH and cirrhosis could lead to the development of targeted therapies that can halt or even reverse liver damage. Such advancements would complement lifestyle interventions and existing treatments, offering patients a broader range of options to manage their liver health [35]. Thus, while current diagnostic approaches offer useful tools for managing liver disease, the future lies in the development of more precise, accessible, and cost-effective diagnostics that can accurately predict disease progression and guide personalized treatment strategies.

CONCLUSION ON ELEVATED AMINOTRANSFERASES AND DIAGNOSTIC APPROACHES

Elevated aminotransferases are a common clinical finding, and their presence demands a thorough and structured evaluation to accurately distinguish between hepatic and extrahepatic causes. While aminotransferases, particularly ALT and AST, serve as vital markers of liver injury, their elevation can be due to a variety of underlying conditions, ranging from liver-specific diseases such as viral hepatitis, alcoholic liver disease, and MASLD, to extrahepatic causes like muscle injury, hemolysis, and thyroid disorders. Therefore, it is crucial to approach the diagnosis in a systematic, stepwise manner. This process typically begins with a detailed patient history and clinical examination, including assessment of lifestyle factors, medication use, and family history. Following this, appropriate laboratory tests, imaging, and, when necessary, liver biopsy, help to narrow down the potential causes of the elevated aminotransferases.

The adoption of a stepwise diagnostic approach, involving both non-invasive markers and more specific tests, plays a pivotal role in ensuring timely diagnosis and appropriate management. Early detection of the underlying cause of elevated aminotransferases, particularly in conditions like MASLD, can significantly influence treatment strategies. For instance, lifestyle interventions such as dietary changes and weight loss can be effective in the early stages of liver disease, preventing its progression to more severe forms like cirrhosis. Furthermore, the timely management of extrahepatic causes such as hypothyroidism or rhabdomyolysis can help alleviate symptoms and prevent complications. By integrating clinical history, laboratory results, and imaging, healthcare providers can make informed decisions that tailor treatments to the individual needs of the patient, improving both short-term outcomes and long-term prognosis.

Importantly, while significant advances have been made in the diagnosis of liver diseases, further research into non-invasive biomarkers for liver function and fibrosis assessment is essential. Non-invasive tools, such as imaging technologies and blood tests, are increasingly being refined to offer a more accurate, cost-effective, and accessible means of diagnosing liver conditions. These innovations could help reduce the reliance on invasive procedures, such as liver biopsies, and provide patients with a more comprehensive understanding of their liver health. However, despite these advancements, early detection remains the cornerstone of effective management, as it allows for timely intervention and the possibility of reversing or slowing the progression of liver disease, particularly in patients with metabolic syndrome or MASLD.

In conclusion, the evaluation of elevated aminotransferases is an essential clinical task that requires a methodical approach to differentiate between various potential causes. The importance of early diagnosis and appropriate management cannot be overstated, as it is crucial in preventing the progression to more severe liver diseases and improving patient outcomes. Continuing advancements in diagnostic tools and treatment strategies hold promise for enhancing the care of patients with elevated aminotransferases, and ultimately, for reducing the global burden of liver disease.

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Corresponding author:

Stamatia Tsoupra
Resident Doctor of Internal Medicine, PhD Candidate
of the Medical School of University of Patras,
Patras, 26504 Greece
Tel.: +30 6944943854, E-mail: stamtsoupra@gmail.com

Rare complications of acute meningococcal sepsis: A case-report and literature review

Dimitrios Bousis[1], Vasileios Karamouzos[1], Virginia Mplani[1], Katerina Zafeiri[1], Alexandra Georgakopoulou[1], Sotiria Kefala[1], Aggeliki Bellou[1], Eirini Zarkadi[1], Markos Marangos[2], Fotini Fligou[1]

Abstract

Acute meningitis and septicemia caused by *Neisseria meningitidis* is a severe bacterial disease with worldwide distribution. In particular, *N. meningitidis* serogroup B predominantly causes meningitis and less frequently is associated with the more severe form of the disease, which can on some occasions become complicated with rare but critical clinical manifestations such as limb ischemia and septic cardiomyopathy. Herein, we present the case of a 20-year-old patient with serogroup B meningococcal septicemia presenting with extensive purpura fulminans, septic shock and septic cardiomyopathy. The patient was treated with antibiotics, high-dose vasopressors, fluids and finally levosimendan due to cardiac dysfunction and hypoperfusion. The patient's condition gradually improved with shock resolution and discontinuation of vasopressor support. Unfortunately, the extensive ischemic lesions on lower extremities led to bilateral leg amputation. The aim of this case-report and literature review is to discuss the complications of invasive meningococcal disease, their management and their impact on the overall prognosis of individuals with meningococcal sepsis.

Key words: *Meningococcal sepsis; meningococcal meningitis; Neisseria meningitidis serogroup B; purpura fulminans; septic cardiomyopathy*

INTRODUCTION

Neisseria meningitidis, commonly referred to as the meningococcus, is a Gram-negative bacterium that appears microscopically as diplococcus, due to its tendency to form pairs [1–3]. It is encapsulated by a polysaccharide layer, which serves as the basis for defining the major serological groups of the bacterium. Among these, types A, B, C, W, X, and Y are those that are more frequently associated with invasive meningococcal disease (IMD) [4–6]. Despite significant progress in rapid diagnostic methods, widespread vaccination campaigns, and the availability of effective antibiotics, IMD continues to pose a serious public health threat. In Europe alone, there were 1,149 confirmed cases and 110 deaths reported in 2022 [7]. The clinical presentation of the disease is typically divided into

Abbreviations: *IV, Intravenous; ER, Emergency Room; CT, Computer Tomography; CSF, Cerebrospinal fluid; gr , Grams; mg, milligrams; pg, Picograms; μg, Micrograms; ICU, Intensive Care Unit; LV, Left ventricle; EF, ejection fraction; Kg, Kilogram; μl, Microlitre; ARDS, Acute Respiratory Distress Syndrome; IMD, Invasive meningococcal disease ; ECMO, Extracorporeal membrane oxygenation; RRT, Renal replacement therapy; SCM, Septic cardiomyopathy; CI, Cardiac index; BNP, B-type natriuretic peptide*

[1]Intensive Care Unit, University Hospital of Patras, Rion, Patras
[2]Clinic of Internal Medicine, University Hospital of Patras, Rion, Patras

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two main forms: the hemodynamic (sepsis) and the neurological (meningitis) [8]. Due to the severity of these conditions, patients often require admission to the intensive care unit (ICU) for close monitoring and supportive management.

In this narrative review, we discuss a series of rare complications that influenced the clinical course and ultimately defined the outcome of a young patient admitted to our ICU, with meningococcal purpura fulminans.

CASE PRESENTATION

A 21-year-old female patient, with no known prior medical history and previously unvaccinated against *Neisseria meningitidis* serotype B, was admitted to the emergency room (ER) of a University Hospital in Greece, after being found unconscious and febrile (up to 40°C). In the ER, she was tachycardic and hemodynamically unstable, necessitating the administration of IV fluids and vasopressors (noradrenalin 0.17 mcg/kg/min and vasopressin 0.07 units/min) to maintain a mean arterial pressure of 65 mmHg. No signs of meningism were evident, likely due to her reduced level of consciousness (GCS 8/15). Her skin exhibited a diffuse maculopapular hemorrhagic rash that did not blanch upon the application of local pressure (Figure 1). The upper and lower extremities were cyanotic and cold. Laboratory investigations indicated multiple-organ damage: elevated liver enzymes, troponin (1478 pg/ml), serum urea, creatinine, prolonged prothrombin, thromboplastin time (PT/PTT respectively) and severe thrombocytopenia. The patient was immediately intubated and administered an initial dose of 2 gr ceftriaxone IV. No abnormalities were detected in the brain computer tomography (CT) scan. Subsequently, a lumbar puncture was performed. The overall examination of the cerebrospinal fluid (CSF) was indicative of acute bacterial meningitis (decreased CSF glucose and elevated protein levels), although the CSF culture returned negative. However, blood cultures obtained prior to ceftriaxone administration were positive with *N. meningitidis* serogroup B. Consequently, individuals who had close contact with the patient within the last 24 hours preceding her admission, and/or worked at the academic institution she attended received chemoprophylaxis with 400 milligrams (mg) ciprofloxacin orally, in accordance with current meningococcal prevention guidelines [9,10].

Within hours of her ER admission, the patient was transferred to the ICU. While being persistently febrile under IV antibiotic treatment with meropenem [2 grams (gr) every eight hours] and vancomycin (1gr twice daily), vasopressor support escalated, and IV hydrocortisone (50mg every six hours) was added to the norepinephrine/vasopressin regimen. The patients' laboratory troponin values increased dramatically, from 1478 picograms (pg)/ml at the time of admission to over 300,000 pg/ml five hours later. The electrocardiogram (ECG) revealed ST elevation in multiple leads (V2-V6, II, III, a VF). Transthoracic ultrasound indicated an ejection fraction (EF) of 15-20%, global hypokinesia and impaired contractility of the left ventricle (LV), with no evidence of pericardial fluid accumulation. Consequently, IV levosimendan was initiated at a dose of 0.08 μg/min/kilogram (kg) of bodyweight and the patient underwent coronary angiography with IV contrast medium, which revealed no obstruction or atheromatosis of the coronary arteries. Three hours after the initiation of IV levosimendan, the EF was measured at 35-40% on a subsequent transthoracic cardiac ultrasound. Overall, hemodynamic stability was restored after 24 hours of IV levosimendan and troponin levels gradually decreased over the following days, while the ECG abnormalities

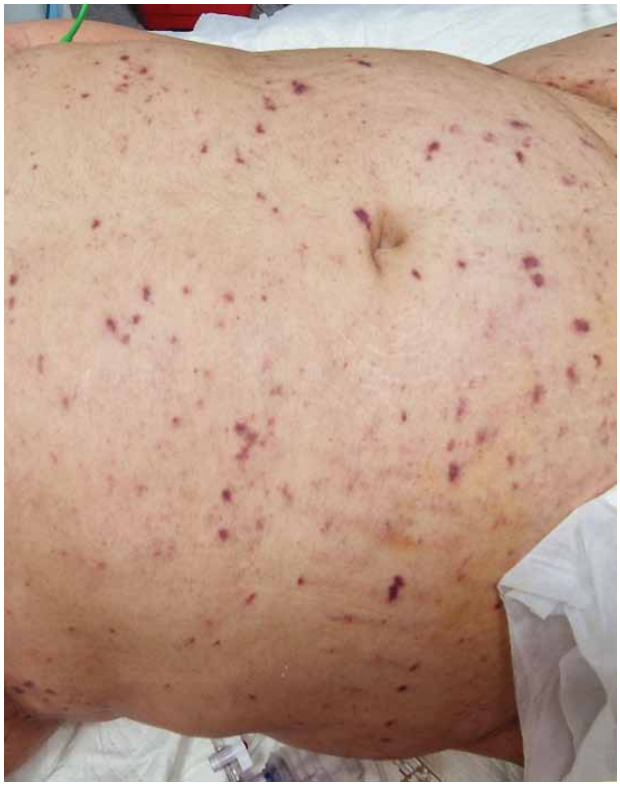

Figure 1. Abdominal purpuric lesions at the time of ER admission.

also gradually resolved. Intravenous vasopressors were discontinued. On the third day of hospitalization, the EF normalized to values over 50%; however, pericardiac fluid up to 0.8 cm in diameter was detected on multiple cardiac ultrasound examinations. Consequently, hydrocortisone was discontinued and colchicine (0.5 mg twice daily) along with ibuprofen (600 mg every 8 hours) was initiated.

The laboratory abnormalities associated with multiple-organ failure gradually returned to normal. Additionally, no evidence of acquired immune deficiency was detected: the HIV test was negative and complement component levels (ch50 test was performed) were within normal the range.

The appearance of the lower extremities did not improve over time. Despite the gradual improvement of the purpuric skin lesions and the slow normalization of coagulation parameters, the hands and feet remained cyanotic and cold, with a difficult-to-detect pulse on the peripheral arteries. Over time, hands returned to normal, but both feet did not show clinical improvement (Figure 2). In accordance with the guidelines on the management of meningococcal purpura fulminans, despite the thrombocytopenia observed the first four days after admission (approximately 50,000/microlitre (μl) platelets), prophylactic regimen with low molecular weight heparin was administered in an attempt to prevent irreversible occlusion of peripheral arteries [11–13]. Multiple doppler ultrasound examinations of peripheral arterial circulation detected active blood circulation bilaterally in the popliteal, radial, ulnar and dorsalis pedis arteries. Further investigation with CT angiography of the abdominal aorta on the fifth day of hospitalization revealed no obstruction in blood supply below the level of abdominal aorta.

Following hemodynamic stabilization, the patient developed acute respiratory distress syndrome (ARDS) on the fifth day of hospitalization, necessitating prone position for 12 hours and a modification of the antibiotic regimen to ceftazidime/avibactam IV and colistimethate (both IV and inhaled). Despite these challenges, the patient was successfully extubated on the ninth day and was transferred to the Department of Internal Medicine of our Hospital. Upon the successful completion of the full antibiotic scheme, she was relocated to a specialized center for the treatment of lower limb lesions. However, the clinical condition of her legs did not improve, ultimately resulting in bilateral amputation below the knees.

Meningococcal disease

Neisseria meningitidis is an obligate human pathogen [5], with the human nasopharyngeal mucosa serving as the sole known ecological niche of N. Meningitidis [14, 15]. Since humans are the only natural host for N. meningitidis, no ideal experimental animal models exist regarding the development of IMD [5].Colonization of the nasopharynx by meningococci is a common occurrence in all age groups, with a peak in incidence observed in adolescents and young adults up to 23 years of age. The overall colonization rate is estimated at approximately 8 –10% of the overall population [1,15–17], with a peak prevalence of 23.7% at the age of 19-years [17].

However, on rare occasions, *N. meningitidis* can evade innate mucosal immunity and progress to a rapidly deteriorating clinical syndrome. This syndrome is char-

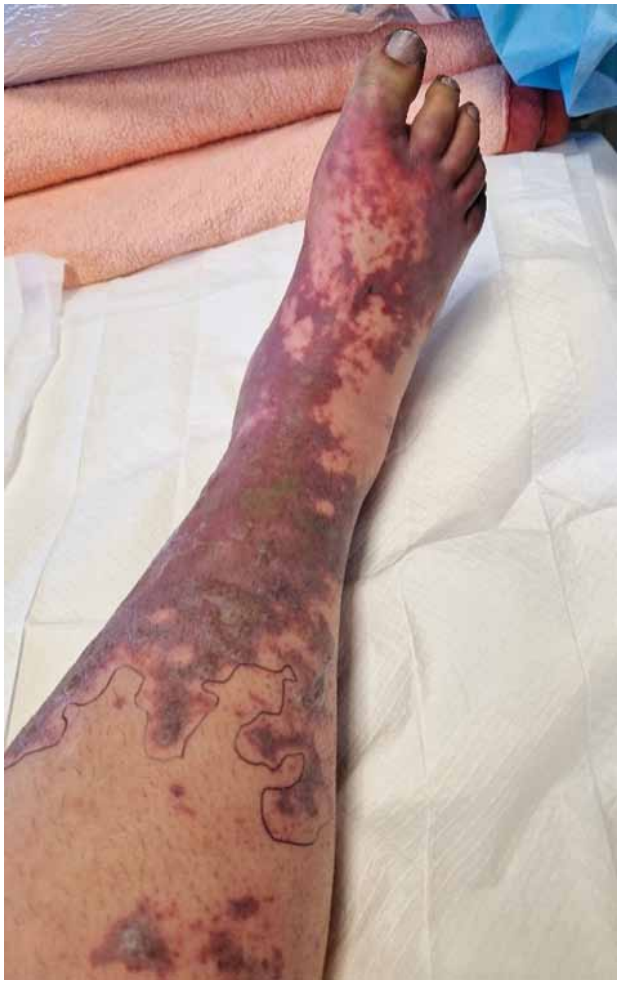

Figure 2. Purpuric and ischemic lesions on the right lower limb.

acterized by the swift dissemination and proliferation of the bacterium within the bloodstream, leading to colonization of peripheral blood vessels. Subsequently, the bacterium may migrate to the central nervous system by crossing the blood-brain barrier [2,14,18]. The precise etiology underlying this severe clinical syndrome in certain individuals remains unclear. The literature suggests that susceptible human carriers may harbour distinct phylogenetic meningococcal groups with increased virulence compared to asymptomatic carriers. Additionally, genetic polymorphisms in the genomes of patients who develop invasive meningococcal disease have been implicated [14].

Overall, the structural characteristics of *N. meningitidis* endow it with numerous mechanisms to evade innate immunity and facilitate meningococcal migration and survival within the bloodstream. Notably, bacterial type IV pili, which adhere to human CD46 [4,5,19] and CD147 [14,18] promote adhesion to the nasopharyngeal mucosa and endothelial cells in peripheral vessels. Furthermore, the bacterial factor H binding protein recruits factor H, a component of the complement activation cascade and along with the bacterial NaIP (a serine protease), inhibits the host's complement activation and deposition of C3b on the meningococcal surface, thereby enhancing survival within human blood vessels [5]. Additionally, *N. meningitidis* is known to increase iron intake from its human host [15], thereby evading intracellular oxidation after macrophage phagocytosis by metabolising L-glutamate to glutathione [14]. Moreover, by binding to endothelial β2-adrenergic receptors, *N. meningitidis* induces structural alterations in the endothelial cytoskeleton on the apical membrane of the human endothelial cells and surrounding trans endothelial junctions. This process facilitates the formation of shear-stress- resistant growing bacterial aggregates, such as biofilm, on the apical surface of the endothelium and the gradual development of progressive endothelial leakage into surrounding tissues. This phenomenon primarily affects small peripheral blood vessels and is considered a critical initial step in the progression to invasive meningococcal septicemia [14, 18, 20]. This mechanism enables the bacterium to reach and traverse the blood-brain barrier. Experimental models involving immune-suppressed mice transplanted with human skin grafts, infected subsequently with *N. meningitidis*, have demonstrated that colonization of human endothelial cells is a necessary precursor to the spread of meningococcal infection to the animal host [20]. Finally, bacterial lipopolysaccharide induces massive activation of the host's immune system, leading to septic shock and multiple-organ failure [14].

Interestingly, although the phase of progressive bacteremia can be completely clinically asymptomatic [14,18], some patients might develop a diffuse purpuric rash due to extensive endothelial damage, which is subsequently complicated with pathologic activation of the coagulation cascade, ultimately resulting in thrombosis, most evident in peripheral blood vessels and capillaries. This severe form of disseminated intravascular coagulation (DIC) is known as purpura fulminans and is frequently associated with immune deficiencies and/or genetic protein C and S deficiency, which can also arise as an acquired consequence of the meningococcal sepsis itself [21–24]. Purpura fulminans is associated with a poor prognosis [21,23].

DISCUSSION

Neisseria meningitidis rarely progresses from mere saprophytic mucosal colonization of the human nasopharynx [14,18] to IMD, which includes meningitis and septicemia complicated with multiple-organ failure [4,25], with a case-fatality rate ranging from 10% to 40% [26]. IMD can be classified as a "rare disease" according to the actual global definition of this term, which categorizes conditions affecting fewer or equal to one person out of 2000 [27,28].

It is known that the capsule of *N. meningitidis* serogroup B is significantly less immunogenic compared to the other predominant serogroups, because its polysaccharide layer mimics the molecular structure of human sialic acid and neural cell adhesion molecules [5]. Interestingly, it accounts for the majority of IMD cases worldwide [4,16,26,29–31], in all age-groups [7,32], with reports dating back from the 1960's [30]. In alignment with global trends, in Greece the majority of meningococcal isolates [33–35] and meningococcal disease cases from 2004 to 2024, about 77.6%, were attributed to *N. meningitidis* serogroup B [36], while further information regarding the incidence of IMD is limited.

In a recent retrospective study by Contou et al., conducted between 2016 and 2024 in 102 French ICUs, 654 patients were admitted with confirmed IMD. Among these, 62% had meningitis and 38% sepsis. In patients with neurological presentation, serogroup B was predominant, whereas serogroup W135 was common in those with hemodynamic presentation. Patients with sepsis compared to those with meningitis had a lower

EF on admission and required more organ support (mechanical ventilation, vasopressors, extracorporeal membrane oxygenation (ECMO), renal replacement therapy (RRT). In-hospital mortality was 4.7% among patients with meningitis and 26.3% among those with sepsis. Among sepsis patients, 20.6% received dobutamine, and limp amputation occurred in 14.8% of hospital survivors [8].

In an older review published by Dastouri F. et al. in 2015, the incidence of limb amputations in IMD survivors was estimated approximately at 2.3% [37]. However, in the subgroup of patients presenting with meningococcal purpura the chances of amputation are higher. Purpura fulminans is characterized by diffuse hemorrhagic skin lesions and focal areas of cutaneous necrosis [21] and is associated with severe dysfunction of the innate coagulation mechanism [11]. *N. meningitidis* and Streptococcus pneumoniae are the most frequent bacterial triggers [21,38]. Although it is considered a direct complication of meningococcal septicemia, it may also represent a separate clinical entity, still closely associated with IMD, based on pathologic findings featuring excessive white blood cell infiltration of peripheral blood vessels and capillaries, which does not occur in purpura fulminans under other clinical circumstances [11,13]. Overall, in patients presenting directly with purpura fulminans, the risk of limb amputation has been reported to be as high as 28.3%, with one-third of these patients being at risk of losing three-quarters of their hand and feet [22–24,39, 40]. Interestingly, the level of skin demarcation and the overall superficial spread of skin necrosis do not necessarily correlate with or indicate the level of amputation that a patient with purpura fulminans might require [41]. Managing purpura fulminans presents a complex challenge, requiring a delicate balance between treating thrombosis and controlling bleeding risks. Patients at low risk of bleeding require heparin and support with blood products (fresh frozen plasma, red blood cells, cryoprecipitate and platelets) [42].The most recent guidelines from the Japanese Society on Thrombosis and Hemostasis recommend the administration of antithrombin and recombinant thrombomodulin [43].

On the other hand, septic cardiomyopathy (SCM), frequently followed by pericarditis, has been the subject of extensive research and usually is underrecognized. It occurs in approximately 28.2% of all cases of septicemia [44], and is thought to result from the toxic effects of various inflammatory mediators and chemokines, combined with pathological β1-adrenergic signaling. This leads to contractile dysfunction and often increased myocardial cell apoptosis [44–46]. To this date, no clear definition or guidelines for the treatment of SCM exist. The suggested approach is to treat sepsis, restore organ perfusion and this will lead to myocardial function improvement. In those patients in septic shock, cardiac dysfunction and hypoperfusion, the "surviving sepsis campaign" guidelines recommend using epinephrine or adding dobutamine to norepinephrine [47]. The combination of septic and cardiogenic shock leads to five distinct patterns, septic shock, septic shock with sepsis induced cardiogenic shock, septic shock on underlying myocardial dysfunction, cardiogenic shock with superimposed septic shock and pure cardiogenic shock. Furthermore, sepsis induced cardiogenic shock can affect the left, the right or both ventricles changing the therapeutic approach [48]. The literature suggests including transthoracic cardiac ultrasound as a standard diagnostic procedure in patients admitted with purpura fulminans, even in the absence of prior cardiologic examination [11]. However, the effects of meningococcal septicemia on the myocardium have been discussed in only a limited number of case-reports presented on Table 1. Levosimendan, a novel inotropic agent that enhances the sensitivity of intracellular tropomyosin C to calcium, thereby improving myocardial contractility, increasing EF, reducing the risk of arrhythmia and promoting local vasodilation within the myocardium, has been considered a potential new therapeutic approach in septic cardiomyopathy. It has been shown to increase blood supply to internal organs, decrease serum troponin and lactic acid levels and facilitate successful weaning in intubated patients [49]. A recent randomized control trial comparing levosimendan to dobutamine in patients with SCM concluded that patients in the levosimendan arm after 72 hours had significantly higher cardiac index (CI), EF and lower levels of B-type natriuretic peptide (BNP) and troponin [50]. However, the limited size of the existing trials does not provide sufficiently strong evidence to establish the beneficial role of levosimendan in septic cardiomyopathy [50,51].

Currently, two vaccines have been developed, targeting primarily the bacterial factor H binding protein, each for different age groups and have been proven effective against serogroup B *N. meningitidis* [29,33,34,52,53]. Their use has been endorsed globally for IMD prevention. As of the time of this writing though, vaccination rates have been declining since the onset of the COVID-19 pandemic, resulting in a concurrent increase in new IMD

Table 1. *Case Reports of patients with meningococcal sepsis and myopericarditis.*

	Age/ Gender	Serogroup	ECHO findings	Inotropes	Time to LVEF recovery	Complications	Outcome
Karamanolis et al. 2025 [55]	39 F	B	EF:20% small pericardial effusion	n/a	6 days	Unilateral hearing loss	Alive
Dawson et al. 2018 [56]	55 F	W	Normal EF, reduced global longitudinal strain, pericardial effusion	n/a	-	-	Alive
Bouneb et al. 2018 [57]	17 M	n/a	EF:35%	n/a	n/a	None	Alive
Steele et al. 2017 [58]	67 M	W	Mild-moderate left ventricular impairment	n/a	n/a	Arthritis	Alive
Woudstra et al. 2016 [59]	71 M	C	EF:30% large pericardial effusion	n/a	3 months	Tamponade-pericardiotomy	Alive
Taldir et al. 2013 [60]	47 M	C	impaired right ventricular contractility		Normal right ventricle after 5 months	None	Alive
Nkosi et al. 2009 [61]	18 M	Y	EF: 25-30% pericardial effusion	n/a	5 days	Tamponade	Alive
Ejlertsen et al. 1988 [62]	19 M	W	Pericardial effusion	n/a	n/a	Tamponade	Alive

cases worldwide despite an initial significant decline at the beginning of the quarantine period [54]. The patient in this case was unvaccinated against *N. meningitidis* serogroup B; however, until 2025 vaccination was recommended only for other predominant meningococcal serogroups in the Greek immunization schedule.

In conclusion, IMD caused by meningococcus serogroup B, although a rare disease, poses a serious health problem worldwide, often resulting in severe disability and death. Myocardial dysfunction and limb ischemia requiring amputation are rare complications with significant impact on patient outcome and quality of life. Therefore, even if infrequent, they should always be considered by physicians in order to achieve optimal clinical outcomes.

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Corresponding author:

Dimitrios Bousis
Intensive Care Unit, University Hospital of Patras, Rion, Patras
Tel.: +30 6972056353, E-mail: dimitrisbousis@gmail.com

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