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Alveolar Hemorrhage and Necrotizing Pancreatitis Secondary to Idiopathic Cryoglobulinemia: A Rare Case of Respiratory and Systemic Complications and Literature Review

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Abstract

Cryoglobulinemia (CB) is an entity defined as the presence of aberrant proteins or immunoglobulins that precipitate at temperatures below 37°C in the blood. Commonly observed in a wide range of illnesses such as infections, haematological, malignancies, and autoimmune disorders, CB may be encountered without a specific aetiology, giving rise to the term "idiopathic" cryoglobulinemia. While typical clinical manifestations encompass skin lesions, arthralgias, neuropathies, and glomerulopathies, this condition may also lead to rare yet severe complications, such as alveolar hemorrhage and gastrointestinal involvement. In this context, we describe an exceptional case involving acute respiratory distress syndrome (ARDS) and necrotizing pancreatitis secondary to idiopathic cryoglobulinemia.

Keywords: Idiopathic Cryoglobulinemia; Mixed Cryoglobulinemia; Alveolar Hemorrhage; Acute Respiratory Distress Syndrome; Vasculitis

Introduction

Cryoglobulinemia (CB) is defined as the persistent presence of abnormal immunoglobulins (Igs) in serum which precipitate at low temperatures (below 37°C) and dissolve upon heating [1]. First identified by Wintrobe and Buell in 1933, then named by Lerner and Watson in 1947, this entity is classified into three subtypes based on the immunoglobulins' (Igs) composition in the serum [2]. Type I CB is characterized by a single class of monoclonal Ig, typically IgM or IgG, and the clinical manifestations are often related to intravascular obstruction, including joint, skin, kidney, and neurological involvement. More frequently, mixed-cryoglobulinemia (MC) implies a combination of monoclonal IgM and polyclonal IgG (type II), or polyclonal IgM and IgG (type III), and the clinical manifestations are generally linked

to deposits of immune complexes [3]. However, CB can also be encountered without a specific etiology, hence the term 'idiopathic' cryoglobulinemia. While typical clinical manifestations include skin lesions, arthralgia, neuropathy, and glomerulopathy, this entity may also result in rare but harsh complications, such as gastrointestinal, central nervous system, cardiac, and pulmonary [4]. Furthermore, no case of pancreatitis in CB has been so far reported. Therefore, we present an exceptional case of an alveolar hemorrhage and necrotizing pancreatitis secondary to cryoglobulinemia and a comprehensive literature review.

Case Presentation

A 39-year-old man was admitted to emergency with dyspnea that had been worsening for a week. He had no other complaints. On history, the patient explained that he felt increasingly breathless, and could only walk a few steps. He had been to see his family doctor, who suspected bacterial bronchitis, for which he was prescribed antibiotics (amoxicillin-clavulanic acid), without much improvement. The patient presented no notable medical or surgical history and did not take medication on a regular basis. However, he mentioned that he was a weightlifter and had been taking anabolic steroids for almost 20 years.

The parameters on arrival were as follows; a blood pressure of 124/74mm Hg, a heartbeat rate of 114 per minute, a temperature of 37°C, an oxygen saturation of 94% with 4 litres of O2, and a respiratory rate of 20 per minute. On clinical examination, cardiac auscultation was normal. However, pulmonary auscultation revealed diffuse rales in both lung fields and crackles at the bases of the lung. Abdominal and neurological examinations were both reassuring. Bearing in mind the patient's condition at the time of consultation, complementary exams were realized.

Arterial blood gas showed a pH of 7.41, pC02 of 32mm Hg, PaO2 of 75mm Hg, and elevated lactate of 3.8mmol/L. An initial blood laboratory revealed a reassuring hemogram, elevated white blood cells of 20,230/mm³ (N 3,5-11,0x10³), markedly elevated inflammatory markers, including a C-reactive protein level of 504.3mg/dL, normal coagulation, acute renal failure with elevated creatinine of 3.82mg/dL (N <1.2), urea of 213mg/dL (N 17-49), uric acid of 19mg/dL (N < 7.2), and altered glomerular filtration rate of 19mL/min/1.73m² (N>60). Disturbance of hepatic enzymes (cytolysis without cholestasis), bilirubin elevated to 2mg/dL (N <1.2) with direct predominance at 1.8mg/dL (<0.2), accompanied by elevated CK at 3,059 U/L and LDH at 987 U/L. Lipase was measured at 86 IU/L (N <60). A pair of blood cultures were taken and a microscopic urine analysis was carried out, both coming back negative. A chest X-ray showed extensive bilateral parenchymal infiltration (figure 1A).

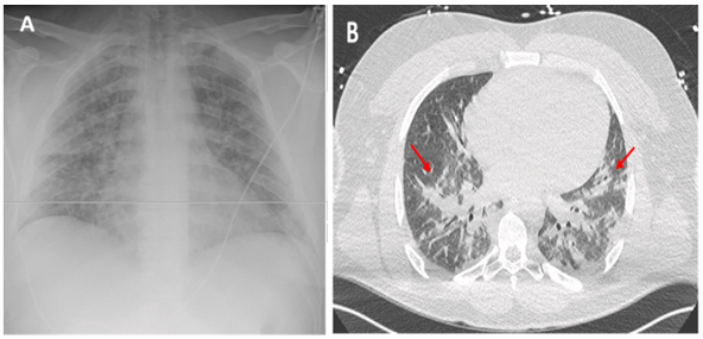

Figure 1: Chest radiography (A) and CT-Scan showing multiple bilateral infiltrates extending to all 2 lings fields (red arrow).

Given the severity of his state, the patient was promptly transferred to the Intensive Care Unit (ICU) on suspicion of acute respiratory distress syndrome (ARDS) with no identified cause. The following days were marked by a rapid deterioration in his respiratory condition, with persistent respiratory acidosis and hypoxemia despite increased oxygen supply via the Optiflow, rapidly necessitating the introduction of mechanical intubation and ventilation. In addition, a veno-venous Extra-Corporeal Membrane Oxygenation (ECMO) was also initiated. A chest CT scan was performed in addition to the workup and revealed multiple bilateral infiltrates extending to all 2 lung fields (figure 1B). Empirical antibiotic treatment was initiated with Moxifloxacin and Dalacin. An additional diagnostic workup was performed; a bronchoalveolar lavage (BAL) revealed significant alveolar hemorrhage without traumatic lesions, and microbiological results were negative despite an extensive panel. Additional biological workup including FAN/ANA, ANCA, Rheumatoid factor (FR), C3-C4, cryoglobulinemia, and extensive infectious serologies (HIV, hepatitis B/C, mycoplasma, leptospirosis, hantavirus) were also performed. The results showed decreased complement factors C3 and C4 despite a significant inflammatory syndrome, negative FAN/ANCA/FR, positive mixed-type cryoglobulinemia, and negative infectious serology. Moreover, a substantial increase in lipase level led to an injected abdominal CT scan demonstrating the presence of acute necrotizing pancreatitis (CTSI score 9) associated with several acute necrotic collections (figure 2). The diagnosis of mixed cryoglobulinemic vasculitis of idiopathic origin complicated by ARDS on alveolar hemorrhage and necrotizing pancreatitis was retained. Systemic corticosteroid therapy was initiated at a dose of 250 mg/day, resulting in clinical, biological, and radiological improvement in the following days. After one week of ICU hospitalization, the patient was successfully weaned off veno-venous ECMO and mechanical ventilation.

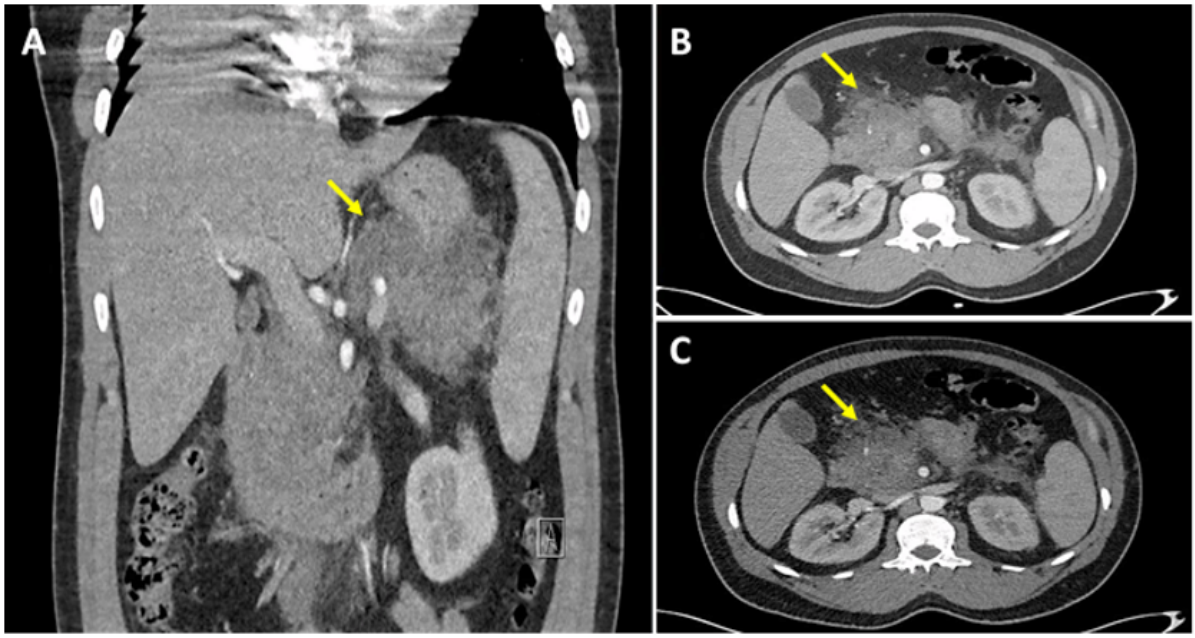

Figure 2: Injected abdominal CT-Scan showing acute necrotizing pancreatitis in coronal (A) and horizontal section (B and C) associated with several acute necrotic collections (Yellow Arrow).

Discussion

Based on the latest epidemiological data, cryoglobulinemia is fairly rare and widespread throughout the world, with southern Europe having a higher prevalence than other parts of the globe; the estimated prevalence is around 1 per 100,000 population [5]. Globally, the disease occurs more frequently among patients in the 45-65 age group, with a peak incidence in women (female/male sex ratio, 2-3 to 1) [6]. Nevertheless, its prevalence may be understated owing to clinical polymorphisms and diagnostic techniques. In fact, this geographical distribution reflects the epidemiology of the hepatitis C virus (HCV), which has a worldwide prevalence of around 3% (1-2% in the northern hemisphere, compared to 4-4.6% in the south) [7]. On the other hand, allergic and autoimmune disorders are generally more widespread in northern European countries [8]. Subsequently, these data imply that different risk factors, such as genetics, infections, and environmental conditions may contribute to the pathogenesis of cryoglobulinemia.

Since its first identification, cryoglobulinemia has been linked to a variety of pathologies, and its spectrum has expanded rapidly. From 1974 onwards, the Brouet classification was adopted to differentiate the various types of cryoglobulinemia based on their chemical and immunological characteristics, and the patient's clinical presentation [9].

Type 1 cryoglobulinemia (10-15%) is characterized by a single type of monoclonal Ig, usually IgM or IgG, occurring more frequently in patients with lymphoproliferative disorders (multiple myeloma, non-Hodgkin lymphoma, Waldenström macroglobulinemia), as well as in the early stages (monoclonal gammopathy of undetermined significance (MGUS)) [10]. Usually, the disease is clinically manifested by symptoms related to hyper-viscosity and intravascular obstruction, such as acrocyanosis, Raynaud's phenomenon, cold-induced urticaria, livedo reticularis, retinal hemorrhages, or worse, gangrene [11]. Mixed cryoglobulinemia (MC), which includes both type II (50-60%) and type III (30-40%), is characterized by the presence of immunocomplexes composed of polyclonal IgG and monoclonal IgM with rheumatoid factor (RF) activity directed against IgG (type II), or polyclonal IgM (type III) [12]. MC is often associated with infections, particularly the hepatitis C virus (HCV) (detected in over 70-80% of cases), autoimmune diseases (Sjogren's syndrome (SS), systemic scleroderma, systemic lupus erythematosus (SLE)), and malignancy, while the clinical manifestations are generally linked to deposits of immune complexes in various tissues [4,13]. Nevertheless, in a very small percentage of cases (less than 10%), systemic cryoglobulinemia occurs without an underlying etiology being found; we then speak of "essential" or "idiopathic" cryoglobulinemia, as diagnosed in our patient [14].

Notwithstanding the lack of a full understanding of cryoglobulinemia's aetiology, several authors have addressed the matter, and three mechanisms are considered to be major pathogenic factors; Chronic immuno-stimulation and lymphoproliferation, producing a high level of Igs which form cryoglobulins, an excess in the production of immune complexes; and inadequate clearance of cryoglobulins or their immune complexes [15,16]. Furthermore, the complement levels are generally low, particularly the C4 and C1q fractions, while C3 is generally normal in CB, reflecting the activation of complement by immune complexes, which plays a key role in pathogenesis by contributing to inflammation and tissue damage [3,16]. However, the C3 level decrease in our patient was problematic [17]. According to the literature, it has been shown that a fall in C3 is associated with a more severe presentation of the disease [18,19].

On the whole, most people with cryoglobulinemia are asymptomatic; the percentage of patients who develop symptoms diverges considerably between 2% and 40-50% [4]. The onset of symptoms is interrelated with the type of cryoglobulinemia defined by Brouet et al [9]. Typical clinical manifestations include skin lesions, arthralgia, neuropathy, and glomerulopathy. According to the literature, purpura, weakness, and arthralgia, also known as Meltzer's triad, are hallmarks of CB that only arise in a minority of patients [20,21]. Nevertheless, this entity may also lead to rare but serious complications, such as central nervous system (CNS), cardiac, gastrointestinal, and pulmonary disorders [19,20].

According to our case, alveolar hemorrhage is a serious but rare CB's complication that has been reported in 3.2% of cases reported in the literature and causes acute respiratory symptoms varying from simple dyspnea to more marked distress, requiring intensive management via mechanical ventilation and intubation [20]. Bilateral infiltrates, ground-glass opacities on CT (Figure 1), and a highly hemorrhagic bronchial alveolar lavage may be observed. Furthermore, gastro-intestinal involvement is also scarce in CB. According to the literature, there are a few cases of abdominal vasculitis in cryoglobulinemia, this rare complication also being a poor prognostic factor in 5% of cases of type III cryoglobulinemia [21]. However, there are currently no cases of necrotizing pancreatitis in cryoglobulinemia, suggesting that abdominal involvement may take different forms, and should be considered in the presence of significant evidence in those patients [19,21]. Consequently, our case is noteworthy and unique in that it demonstrates 2 rare complications of cryoglobulinemia in the same patient, without any underlying etiology being found (idiopathic).

The evolution and outcome of cryoglobulinemia vary considerably from one individual to another, reflecting the different types of organ damage that may occur, and influencing the survival's prognosis [15,16].

The management of cryoglobulinemia depends primarily on its etiology. If an etiology is identified, targeted treatment should be initiated. At present, corticosteroid therapy remains the cornerstone of treatment [22]. In recent years, there has been some evidence in favor of antiCD20 monoclonal antibody therapy with rituximab (RTX) in the various types of cryoglobulinemia, but questions about the safety of this therapeutic approach, particularly in HCV patients are lacking, and no consensus has yet been reached [23]. In our patient, intensive support via mechanical ventilation and the use of veno-venous ECMO have been crucial in managing acute respiratory failure and providing support during the critical phase of the disease. Systemic corticosteroid therapy also proved effective in reducing systemic inflammation and treating associated complications. Rituximab was introduced at a later stage and showed good tolerability and clinical-biological and radiological efficacy.

Conclusion

In conclusion, this case emphasizes the importance of considering cryoglobulinemia in patients presenting with diverse systemic manifestations. The diagnostic process involves a thorough clinical evaluation supported by laboratory tests, imaging studies, and sometimes tissue biopsies. While the detection of cryoglobulins in the serum remains a cornerstone in diagnosis, the complexity and variability of clinical presentations underscore the need for a multidisciplinary approach. Clinicians should maintain a high index of suspicion for cryoglobulinemia, especially when encountering uncommon complications such as alveolar hemorrhage and necrotizing pancreatitis. Early recognition and initiation of appropriate therapy, can reduce the morbidity and mortality associated with this challenging condition.

Disclosure and Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Patient: Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Data Availability Statement: The data used and analyzed in this study are available from the corresponding author on reasonable request.

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