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(CASE REPORT)

Association between monoclonal gammopathy and dilated cardiomyopathy: A case report in an adolescent

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Abstract

We report the case of a 14-year-old adolescent presenting a novel association between monoclonal gammopathy and dilated cardiomyopathy (DCM). This clinical case, remarkable for its rarity, highlights a potential pathological link between these two entities.

The patient initially presented with signs indicative of progressive heart failure, including significant fatigue, exertional dyspnea, and peripheral edema. Cardiac investigations confirmed the diagnosis of DCM with a significantly reduced left ventricular ejection fraction, reflecting severe systolic dysfunction.

Simultaneously, biological analyses revealed the presence of a monoclonal spike on serum protein electrophoresis, confirmed by immunofixation as a specific type of immunoglobulin (Ig). The origin of this monoclonal gammopathy remained undetermined despite extensive investigations before the patient's death during her short hospital stay.

Keywords: Monoclonal Gammopathy; Dilated Cardiomyopathy; Adolescent

1. Introduction

Monoclonal gammopathies are a group of disorders characterized by the uncontrolled proliferation and accumulation of plasma cells, leading to the overproduction of monoclonal immunoglobulin (Ig) proteins. [1] These proteins are commonly referred to as monoclonal proteins, M proteins, M spikes, paraproteins, or immunoglobulinopathies, and can be detected in the serum or urine of patients. [2]

In many cases, monoclonal gammopathy results from an underlying malignancy referred to as plasma cell dyscrasia. In other cases, it results from benign clonal expansion without symptoms, termed monoclonal gammopathy of undetermined significance (MGUS). [3] It has been reported that MGUS, MM, and AL amyloidosis are the most common monoclonal gammopathies. [4]

A study conducted in 2003 demonstrated that plasma cell disorders account for 7% of all hematologic malignancies, with approximately 14,000 new cases observed annually in the United States. [5]

Thus, in adolescents, monoclonal gammopathies are rare and unusual. A retrospective analysis revealed the presence of monoclonal gammopathy in serum samples from 79 pediatric patients out of 4,000 (1.9%). [6]

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Dilated cardiomyopathy (DCM), on the other hand, is a severe disease of the cardiac muscle characterized by left ventricular dilation and systolic dysfunction. It can progress to severe heart failure and become life-threatening. [7] However, an association with monoclonal gammopathy (MG) is scarcely documented in the scientific literature.

We report here the case of a 14-year-old adolescent presenting a novel association between monoclonal gammopathy and dilated cardiomyopathy (DCM). This clinical case, remarkable for its rarity, highlights a potential pathological link between these two entities.

2. Case observation

This case concerns a 14-year-old adolescent with a medical history of neonatal respiratory distress, recurrent respiratory infections with bronchiectasis (BE), and growth retardation. The patient's family reported no known hereditary diseases or instances of sudden family death.

The symptoms began two months before admission with the onset of stage III dyspnea, accompanied by cough and sputum production, prompting a consultation at a private healthcare facility. A transthoracic echocardiogram (TTE) performed at that time revealed dilated cardiomyopathy (DCM) with severe dysfunction, a left ventricular ejection fraction (LVEF) of 32%, moderate mitral regurgitation (MR), a dilated left atrium (LA), cardiomegaly, and pericardial effusion.

One month before admission, the symptoms worsened, with the appearance of stage IV dyspnea associated with orthopnea and lower limb swelling. No other associated symptoms were reported (no palpitations, syncope, or presyncope). This progression occurred in an afebrile context with a decline in general health.

Upon clinical examination, the patient was conscious, pale, normotensive (112/73 mmHg), tachycardic (115 bpm), and tachypneic (22 breaths per minute). She weighed 34 kg (-2 SD), had a body temperature of 37.1 °C, and an oxygen saturation of 97% in ambient air.

The cardiovascular examination revealed jugular venous distention (JVD) and hepatojugular reflux (HJR), as well as lower limb edema (white, soft, pitting, painless, and limited to the feet). The apex beat was displaced and diffuse. Pulmonary examination revealed bilateral basal crackles and signs of basal pleural effusion on the left side.

A chest X-ray showed a bilateral bronchial syndrome and cardiomegaly. A TTE at admission confirmed hypokinetic cardiomyopathy in the dilated stage with severe biventricular dysfunction, an LVEF of 19%, moderate MR, a dilated LA, a dilated inferior vena cava, and a thin layer of pericardial effusion.

Blood analyses showed normal uremia (0.64 g/L), normal creatinine levels (7 mg/L), normal natremia (138 mmol/L), low chloridemia (84 mmol/L), normal kalemia (4.5 mmol/L), metabolic acidosis with HCO_3^- at 16 mmol/L, normal corrected calcemia (88 mg/L), normal phosphatemia (26.88 mg/L), elevated C-reactive protein (54 mg/L), elevated procalcitonin (2.5 ng/mL), normal ferritin (155 ng/mL), elevated alanine aminotransferase (119 U/L), elevated alkaline phosphatase (142 U/L), elevated gamma-glutamyltransferase (151 U/L), elevated total bilirubin (37.69 mg/L), elevated lactate dehydrogenase (705 U/L), normal thyroid-stimulating hormone (2.4 mIU/L), normal thyroxine or T4 levels (19.41 pmol/L), decreased albumin (31 g/L), normal creatine phosphokinase (97 U/L), normal lipase (28.78 U/L), and negative troponin (39.5 pg/mL).

The complete blood count revealed normal leukocyte count (12.96 G/L), elevated neutrophils (11.16 G/L), reduced lymphocytes (0.5 G/L), reduced eosinophils (0.02 G/L), reduced basophils (0.02 G/L), normal monocyte count (0.6 G/L), thrombocytopenia (150 G/L), reduced hematocrit (31.6%), normal erythrocyte count (4.7 million/mm^3), and hypochromic microcytic anemia (hemoglobin: 10.1 g/dL, mean corpuscular volume: 67.2 fL, mean corpuscular hemoglobin: 21.5 pg, mean corpuscular hemoglobin concentration: 32 g/dL).

The coagulation profile showed reduced prothrombin time (41.6%), an elevated international normalized ratio (INR, 1.78), and normal activated partial thromboplastin time (29.4 seconds).

Plasma protein electrophoresis (PPE), illustrated in Figure 1, revealed hypoproteinemia associated with an inflammatory syndrome, along with a monoclonal spike located in the gamma globulin region quantified at 3 g/L.

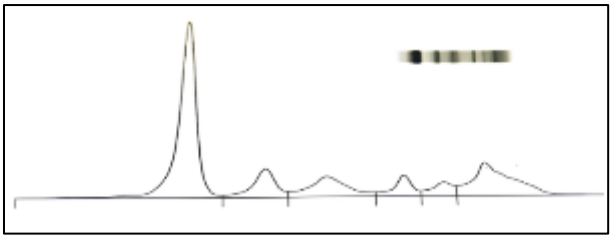

Figure 1 Capillary electrophoresis of serum proteins showing a monoclonal spike in the gamma globulin region

The immunofixation analysis, illustrated in Figure 2, confirmed the presence of a monoclonal immunoglobulin of the IgG-kappa type.

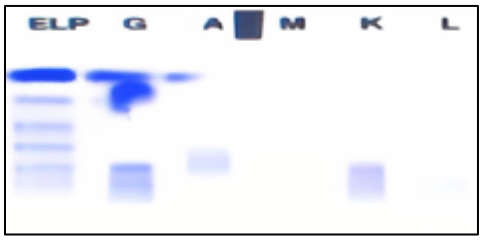

Figure 2 Electrophoresis with serum immunofixation showing the monoclonal Immunoglobulin (Ig) of the IgG-kappa type

The tests for anti-beta-2-glycoprotein-1 antibodies, rheumatoid factor, anti-ENA antibodies (anti-SSB, anti-Sm, anti-RNP, anti-Jo-1, anti-Ro52, anti-SS-B, anti-Scl-70, anti-Ro60), anti-native DNA antibodies, and anti-cardiolipin antibodies (IgM and IgG) all returned negative.

The allergy workup revealed elevated total IgE (131.29 kU/L) and total IgG (25.196 g/L), with a normal level of total IgA (3.002 g/L).

Further investigations were planned to determine the etiology of the DCM and the monoclonal gammopathy, but unfortunately, the patient passed away following a cardiocirculatory arrest.

3. Discussion

While monoclonal proteins can be detected in rare cases among young patients, malignant plasma cell disorders associated with these proteins remain exceptionally uncommon in this population [8]. Indeed, such disorders account for less than 1% of all reported cases of malignant plasma cell disorders [9].

This clinical case highlights two rare pathologies in this age group, the association of which raises several pathogenic hypotheses. Although monoclonal gammopathies are often considered benign monoclonal gammopathies of undetermined significance (MGUS) in young patients [10].

In approximately 66% of pediatric DCM cases, the cause is idiopathic or remains unidentified despite extensive investigations [11]. Familial predisposition or specific genetic mutations are implicated in 20% to 48% of familial DCM cases, with variable transmission, often manifesting clinically in adulthood [11], although sporadic cases are observed in infants [12]. One such genetic mutation identified in a genomic study responsible for neonatal DCM concerns the TTR (transthyretin) gene, which was identified in the context of neonatal DCM [13]. Genetic impairment of the TTR gene is responsible for two forms of amyloidosis: hereditary transthyretin amyloidosis (ATTRv) and wild-type transthyretin amyloidosis (ATTRwt) [14]. Transthyretin cardiac amyloidosis is an increasingly recognized cause of advanced cardiomyopathy requiring evaluation for heart transplantation [15].

ATTRv presents a wide range of clinical manifestations that vary according to age at onset, organ involvement, and disease severity. In contrast, wild-type transthyretin amyloidosis (ATTRwt) is an acquired disease that primarily affects the heart, develops with age, and typically occurs in men over 60 years old.

Transthyretin amyloidosis (TTR) or light-chain (AL) amyloidosis are the two types most commonly associated with restrictive cardiomyopathy [16][17]. The incidence of atypical phenotypes, including dilated cardiomyopathy, associated with TTR amyloidosis remains poorly characterized.

A retrospective study published by the European Society of Cardiology, identified three explants with amyloid deposition and a dilated cardiomyopathy phenotype as observed on pre-transplant echocardiograms. This study concluded that some individuals might have a genetic predisposition to developing cardiac amyloidosis with a dilated phenotype [14].

TTR gene mutations linked to monoclonal gammopathy and DCM are rare and usually appear later in life; however, this mechanism remains possible in our patient despite no known family history or genetic confirmation.

A history of recurrent neonatal respiratory infections could potentially play a role in the development of DCM following chronic viral myocarditis (cytomegalovirus, human immunodeficiency virus, etc.), which accounts for 16% of DCM cases. [18]

Chronic antigenic stimulation, evolving into monoclonal plasma cell hyperplasia, could result from an underlying common variable immunodeficiency (CVID) [6], one of the most common primary immunodeficiencies in Europe, which can manifest at any age, from early childhood to late adulthood [19]. CVID is characterized by a quantitative or functional deficiency in immunoglobulins, predisposing individuals to recurrent respiratory infections and chronic inflammation.

In the context of recurrent infections due to secondary immunodeficiency caused by the human immunodeficiency virus (HIV), HIV-infected patients present with B-cell hyperplasia, circulating immune complexes, elevated autoantibodies, and hypergammaglobulinemia, with approximately 20% of antibodies being HIV-specific [20]. Among HIV-infected patients, hypergammaglobulinemia and a high number of activated B-cells have been identified. In infants vertically infected with HIV, hypergammaglobulinemia is one of the most consistent abnormalities and generally the first to be observed, with elevated serum concentrations of IgG, IgA, and IgM [21]. The IgG hypergammaglobulinemia observed in our patient provides further support for this diagnostic hypothesis.

In a study published by Amara et al., they reported on 25 adult HIV-infected patients in whom a monoclonal paraprotein was detected in the serum, which, according to the authors, corresponded to monoclonal gammopathy of undetermined significance (MGUS) [22]. Ouedraogo et al. identified 21 HIV-infected patients with monoclonal proteins, noting that their ages (20–58 years) were younger than typically observed in the general population, where monoclonal gammopathy usually appears after age 50.[23].

Cardiac disease in HIV-infected children may result from immune mechanisms or opportunistic infections and can manifest as myocarditis, cardiomyopathy, heart failure, or conduction disorders, diagnosed through clinical signs and echocardiography.[24] [18].

Primary cytomegalovirus (CMV) infection in immunocompetent individuals often goes unnoticed, as it is generally asymptomatic. Mononucleosis, the primary syndrome associated with this infection, presents with a lesser degree of tonsillitis, lymphadenopathy, and pharyngitis compared to that caused by Epstein-Barr virus (EBV) [25]. However, lymphocytosis with atypical lymphocytes, commonly seen in primary CMV infection, was not found in our patient.

A monoclonal immunoglobulin was detected by immunofixation electrophoresis in 10 of the 25 immunocompetent patients (40%) aged 17 to 62 years (mean age: 31.8 years) with acute or recent primary CMV infection (ranging from 1 to 3 months old). The presence of the monoclonal immunoglobulin showed no association with the patients' age [26]. In the absence of biological, microbiological, and molecular tests to identify the potential infectious agent, this pathogenic hypothesis remains plausible.

4. Conclusion

This case highlights the rare association of monoclonal gammopathy with pediatric DCM. Possible mechanisms include TTR mutation, viral infection, or immunodeficiency, though no genetic or pathological confirmation was obtained.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest related to the content of this manuscript.

Statement of ethical approval

This research work does not include any experiments or studies involving human participants or animals conducted by any of the authors.

Informed consent was obtained from all individual participants included in the study.

Statement of informed consent

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