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Osteoarticular Manifestations in Primary Immunodeficiency Disorders: A Case Series of Three Patients

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Abstract

Primary immunodeficiency disorders (PIDs) comprise a heterogeneous group of inherited disorders characterized by qualitative and/or quantitative defects affecting one or more components of the immune system. In addition to recurrent infections, musculoskeletal manifestations, particularly arthritis, may occur and occasionally represent the initial presentation of these disorders. Osteoarticular involvement has been reported predominantly in patients with humoral immunodeficiencies, including X-linked agammaglobulinemia, common variable immunodeficiency (CVID), hyper-IgM syndrome, and selective IgA deficiency. We report a case series of three patients with primary immunodeficiency disorders who developed osteoarticular manifestations during follow-up. The first patient, diagnosed with X-linked agammaglobulinemia, presented with aseptic knee arthritis. The second patient, with common variable immunodeficiency, developed probable bilateral infectious arthritis of the knees. The third patient, diagnosed with late-onset combined immunodeficiency (LOCID), presented with acute inflammatory arthralgia involving both knees and ankles, without clinical or ultrasonographic evidence of arthritis. All patients received intravenous immunoglobulin replacement therapy combined with appropriate medical treatment, resulting in favorable clinical outcomes without permanent joint sequelae. These cases highlight the broad spectrum of osteoarticular manifestations associated with primary immunodeficiency disorders and emphasize the importance of early diagnosis and prompt management to prevent irreversible joint damage.

Keywords

Primary Immunodeficiency Disorders, Arthritis, Osteoarticular Manifestations, Intravenous Immunoglobulin, Case Series

1. Introduction

Primary immunodeficiency disorders (PIDs) are caused by qualitative and/or quantitative abnormalities affecting one or more components of the immune system. They may involve humoral immunity (B lymphocytes), cellular immunity (T lymphocytes), combined immune deficiencies, phagocytic dysfunction, or complement deficiencies [1].

PIDs are most commonly characterized by recurrent infections, including common bacterial infections, atypical infections involving unusual pathogens or sites, and opportunistic infections caused by organisms that are usually non-pathogenic. Osteoarticular involvement may also occur during the course of PIDs and may even represent the initial manifestation of the disease [1].

Joint manifestations in PIDs result from various pathogenic mechanisms and have been reported in different types of primary immunodeficiency disorders, particularly humoral immunodeficiencies, including X-linked agammaglobulinemia, common variable immunodeficiency (CVID), hyper-IgM syndrome, and selective IgA deficiency [1].

We report three cases of patients with primary immunodeficiency disorders who developed osteoarticular manifestations.

2. Case 1

A 4-year-old boy with X-linked agammaglobulinemia (Bruton disease), diagnosed at the age of 15 months based on profound hypogammaglobulinemia (IgG: 0.40 g/L, IgA: <0.10 g/L, IgM: <0.08 g/L) and absent circulating CD19+ B lymphocytes, was receiving regular monthly intravenous immunoglobulin (IVIG, 500 mg/kg every 4 weeks) replacement therapy, with occasional treatment interruptions due to limited financial resources. At the time of osteoarticular presentation, immunological evaluation showed an IgG level of 4.49 g/L, IgA < 0.09 g/L, IgM < 0.07 g/L, with persistently absent circulating CD19+ B lymphocytes. He was admitted for right knee pain. His medical history included respiratory distress on the first day of life, bacterial meningitis at the age of one year, and recurrent respiratory tract infections.

The initial episode of right knee pain responded well to antibiotic and analgesic therapy. One month later, the patient developed inflammatory pain in the left knee. Physical examination revealed no swelling of the right knee but limited flexion, whereas the left knee was swollen with a flexion contracture and a heel-to-buttock distance of 16 cm, without overlying inflammatory signs.

Laboratory investigations showed a white blood cell count of 15,460/mm^3, thrombocytosis (664,000/mm^3), and anemia, while both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were within the normal range.

Ultrasonography demonstrated findings consistent with left knee arthritis associated with joint effusion. Joint aspiration yielded a hemorrhagic synovial fluid containing 80% neutrophils and 20% lymphocytes. Direct microscopic examina-

tion and synovial fluid culture were negative, and blood cultures remained sterile. Polymerase chain reaction (PCR) testing for Mycoplasma species was not available at our institution and therefore was not performed.

A diagnosis of aseptic arthritis was established. Empirical antibiotic therapy targeting Mycoplasma species was initiated because Mycoplasma is a well-recognized cause of arthritis in patients with humoral primary immunodeficiency, despite negative conventional microbiological investigations. The patient also received analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and intravenous immunoglobulin replacement therapy.

The clinical outcome was favorable, with complete resolution of pain and regression of joint swelling without residual articular sequelae.

3. Case 2

A 23-year-old woman with common variable immunodeficiency (CVID), diagnosed on the basis of hypogammaglobulinemia (IgG: 1.2 g/L, IgA: 0.11 g/L, and IgM: 0.10 g/L), had a history of recurrent respiratory tract infections since early childhood, complicated by bronchiectasis diagnosed at the age of 12 years. She had been receiving regular monthly intravenous immunoglobulin (IVIG, 500 mg/kg every 4 weeks) replacement therapy, with occasional treatment interruptions due to limited availability of immunoglobulin and financial constraints, for the past four years.

She was admitted following hospitalization for an exacerbation of bronchiectasis because of the acute onset of severe bilateral knee pain. Physical examination revealed swelling of both knees, associated with local inflammatory signs and marked pain during both active and passive movements.

Laboratory investigations showed a white blood cell count of 7700/mm^3, including 4300/mm^3 neutrophils, a C-reactive protein (CRP) level of 77 mg/L, and an erythrocyte sedimentation rate (ESR) of 20 mm/h.

Radiological assessment revealed millimetric collections in both knees associated with soft tissue infiltration of the calves and minimal joint effusion.

Blood cultures remained sterile. Joint aspiration was not performed because of the small size of the collections, precluding microbiological culture and polymerase chain reaction (PCR) testing for *Mycoplasma* species. Despite the absence of microbiological confirmation, the diagnosis of probable infectious arthritis was considered based on the clinical presentation, inflammatory biological findings, and imaging features.

The patient received empirical antibiotic therapy targeting *Mycoplasma* species because *Mycoplasma* is a well-recognized cause of arthritis in patients with humoral primary immunodeficiency, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), knee immobilization using splints, and intravenous immunoglobulin replacement therapy.

The clinical outcome was favorable, with complete resolution of knee pain and swelling and no residual joint sequelae.

4. Case 3

A 9-year-old boy with autoimmune hemolytic anemia associated with late-onset combined immunodeficiency (LOCID), diagnosed on the basis of hypogammaglobulinemia (IgG: 1.0 g/L, IgA: 0.08 g/L, and IgM: 0.13 g/L), was followed for recurrent respiratory tract infections and was receiving regular monthly intravenous immunoglobulin (IVIG, 500 mg/kg every 4 weeks) replacement therapy, with occasional treatment interruptions due to limited availability of immunoglobulin and financial constraints.

He was admitted because of the acute onset of functional impairment of the lower limbs associated with arthralgia involving both ankles and knees, predominantly on the right side, with radiation along the right leg. These symptoms were accompanied by a low-grade fever (38˚C).

On musculoskeletal examination, both knees and ankles were free of swelling or local inflammatory signs.

Laboratory investigations showed a white blood cell count of 4730/mm^3, including 3190/mm^3 neutrophils, while both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were within the normal range. Joint ultrasonography showed no abnormalities. Blood cultures remained sterile. Polymerase chain reaction (PCR) testing for *Mycoplasma* species was not available at our institution and therefore was not performed.

The diagnosis of inflammatory arthralgia was retained after exclusion of septic arthritis. Empirical clarithromycin therapy was initiated because *Mycoplasma* species are well-recognized causes of osteoarticular manifestations in patients with primary immunodeficiency despite negative conventional microbiological investigations. The patient also received analgesics, lower-limb immobilization using a splint, and intravenous immunoglobulin replacement therapy.

The clinical outcome was favorable, with complete resolution of pain.

5. Discussion

Osteoarticular manifestations, most commonly arthritis, are mainly observed in patients with humoral primary immunodeficiency disorders (PIDs). They usually present as monoarthritis or oligoarthritis and, less frequently, as polyarthritis that may clinically resemble rheumatoid arthritis [1].

Among these arthritides, some are clearly infectious, whereas others are considered aseptic. In the absence of definitive evidence of infection, an immune-mediated synovial inflammatory reaction has been proposed as the underlying pathogenic mechanism [2].

In humoral PIDs, the reported prevalence of arthritis ranges from 5% to 40% before the initiation of specific treatment [3].

X-linked agammaglobulinemia is a rare disorder, affecting approximately 1 in 50,000 live male births, characterized by profoundly reduced serum immunoglobulin levels and the absence of circulating B lymphocytes due to defective B-cell maturation. Osteoarticular manifestations occur in approximately 20% of pa-

tients, whereas septic arthritis accounts for only 2% - 4% of cases. The majority of cases are aseptic, and osteoarticular manifestations are more frequently observed in humoral PIDs than in other forms of primary immunodeficiency [4].

Approximately 10% - 30% of arthritis cases occurring in patients with humoral PIDs are considered aseptic. Similar to our first patient, aseptic arthritis appears to be more common in children and in patients with agammaglobulinemia, particularly those with serum IgG levels below 8 g/L [4].

Treatment generally relies on intravenous immunoglobulin (IVIG) replacement therapy, which usually results in rapid clinical improvement. In these patients, antibiotic therapy targeting *Mycoplasma* species is also recommended, regardless of whether the organism is isolated by culture or polymerase chain reaction (PCR) from synovial specimens. The clinical course is variable, ranging from spontaneous resolution, as observed in our first patient, to disabling arthritis with significant radiological joint damage.

Common variable immunodeficiency (CVID) is characterized by impaired immunoglobulin production, resulting in hypogammaglobulinemia, most commonly due to reduced IgG levels associated with decreased IgA and/or IgM concentrations. Recurrent respiratory tract infections represent the most common clinical presentation of CVID [5].

Other infections may also occur, particularly urogenital infections, pulmonary infections caused by *Mycoplasma* species, and osteoarticular infections [6].

Septic arthritis in patients with PIDs most commonly presents as monoarthritis or oligoarthritis, as illustrated by our second case. The pathogens most frequently involved are encapsulated bacteria, particularly *Staphylococcus aureus* and *Streptococcus pneumoniae*, reflecting the profound deficiency of IgG2. However, *Mycoplasma* species remain the microorganisms most commonly associated with arthritis in these patients, especially *Ureaplasma urealyticum* and, less frequently, *Mycoplasma pneumoniae*, *Mycoplasma hominis*, and *Mycoplasma salivarium* [7].

In contrast, our third patient presented with inflammatory arthralgia without clinical, biological, or ultrasonographic evidence of septic arthritis, illustrating the heterogeneous spectrum of osteoarticular manifestations in primary immunodeficiency disorders. Biological inflammatory markers may be elevated but are not consistently present, as observed in our third patient.

The three cases illustrate the heterogeneous spectrum of osteoarticular manifestations in primary immunodeficiency disorders. The first patient presented with aseptic arthritis, the second with probable infectious arthritis, and the third with inflammatory arthralgia without objective evidence of arthritis. These distinct presentations required individualized management, although all patients benefited from intravenous immunoglobulin replacement therapy combined with appropriate supportive treatment and empirical anti-*Mycoplasma* therapy when clinically indicated.

Furr *et al*. identified *Mycoplasma* species in 38% of arthritis cases associated with hypogammaglobulinemia, highlighting their major role in this setting. The

mechanisms underlying this particular susceptibility remain poorly understood [7].

Antibiotic therapy targeting *Mycoplasma* species should be initiated even when microbiological cultures are negative. Intravenous immunoglobulin replacement therapy should be administered concomitantly, although its efficacy may be inconsistent because commercially available immunoglobulin preparations contain relatively low concentrations of anti-*Mycoplasma* antibodies. Nevertheless, most reported cases occur in patients with profound hypogammaglobulinemia [8].

Recent evidence has further highlighted the broad spectrum of musculoskeletal manifestations associated with common variable immunodeficiency and other primary antibody deficiencies, emphasizing the importance of early recognition and appropriate multidisciplinary management of these complications [9] [10].

This case series has several limitations. The small sample size limits the generalizability of our findings. In addition, microbiological confirmation was incomplete because polymerase chain reaction (PCR) testing for Mycoplasma species was unavailable and microbiological confirmation could not be achieved in all cases. Finally, although all patients showed favorable short-term clinical outcomes without residual joint sequelae, longer follow-up would be valuable to better assess long-term musculoskeletal outcomes.

6. Conclusion

Early recognition of osteoarticular manifestations in patients with primary immunodeficiency disorders is essential to prevent irreversible joint damage. Intravenous immunoglobulin replacement therapy remains the cornerstone of treatment and should be combined with antibiotic therapy targeting *Mycoplasma* species in patients presenting with recent-onset arthritis, even in the absence of microbiological confirmation. Although this therapeutic approach is not universally established, it appears justified in patients with primary immunodeficiency disorders.

Ethics Statement

Ethics approval for this study was obtained from the Ethics Committee of Mohammed First University, Oujda, Morocco. Written informed consent for publication was obtained from the adult patient and from the parents or legal guardians of the pediatric patients. All patient data were anonymized to ensure confidentiality.

Previous Presentation

This manuscript has not been previously presented at any scientific meeting and has not been published, in whole or in part.

Author Contributions

Yassine Sbia: Conceptualization, study design, patient management, data collection, literature review, manuscript drafting, and final approval of the manuscript. **Aziza El Ouali**: Patient management, data collection, critical revision of the man-

uscript, and final approval. **Abdeladim Babakhouya**: Clinical supervision, critical revision of the manuscript, and final approval. **Maria Rkain**: Clinical supervision, critical revision of the manuscript, and final approval. **Noufissa Benajiba**: Study supervision, critical revision of the manuscript, and final approval.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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