

CASE REPORT

Simultaneous diagnosis of adult-onset Still's disease and lymphoma: A case report and systematic review of the literature

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Key Clinical Message

Differentiating Adult-Onset Still's Disease (AOSD) from lymphoma is challenging. A 23-year-old female presented with polyarthralgia, fever, rash, lymphadenopathy, and abnormal labs. She met AOSD criteria and was diagnosed with non-Hodgkin lymphoma. Treatment led to improvement.

Abstract

The differentiation between Adult-onset Still's Disease (AOSD) and lymphoma remains challenging in our context. The Faustrel score facilitates the simultaneous diagnosis of these conditions. A 23-year-old woman presented with chronic polyarthralgia in a febrile context. A physical examination revealed peripheral joint syndrome, a maculopapular rash on the trunk, and peripheral lymphadenopathy. Laboratory tests showed neutrophils leukocytosis, hyperferritinemia, and a glycosylated ferritin fraction of 12%. A lymph node biopsy revealed a malignant non-Hodgkin lymphoma, and the patient met the diagnostic criteria for AOSD according to Faustrel. She received corticosteroid therapy and four courses of Rituximab. After 6 months, clinical and biological improvements were noted. It is essential to consider the possibility of an association between atypical clinical presentations of lymphoma and AOSD.

KEYWORDS

adult-onset Still's disease, ferritin, glycosylated ferritin fraction, lymphoma

1 | INTRODUCTION

In 1971, Bywaters described the first cases of AOSD, a clinical entity considered to be the adult equivalent (i.e.,

in patients over 17 years of age at onset) of systemic juvenile idiopathic arthritis described by Still a century ago.¹ Adult-onset Still's disease (AOSD) is a rare autoinflammatory condition resulting from a multigenic interaction,

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with an incidence of 1 to 34 cases per million inhabitants, generally with a good prognosis.² AOSD and lymphomas exhibit notable clinical similarities, making it challenging to differentiate between these two conditions. Confirming a diagnosis of AOSD requires the exclusion of infectious, hematologic, autoimmune, and neoplastic causes.³ However, a more recent scoring system, the Faustrel score, does not require exclusion criteria; it has a sensitivity of 80.6% and a specificity of up to 98.5%, which is superior to the Yamaguchi score.² The Faustrel score considers glycosylated ferritin and does not account for exclusion criteria, allowing for the diagnosis of such an association. In medical literature, the association between AOSD and lymphoma is rarely described, with even fewer reports of the simultaneous diagnosis of these conditions. This study describes a concurrent diagnosis of AOSD and lymphoma in a patient.

2 | CASE REPORT

2.1 | Case history

A 23-year-old woman patient, nulligravida, no tobacco or drug history and no personal or familial pathological history, presented with polyarthralgia affecting both large and small joints, occurring intermittently for the past 8 months, accompanied by recurrent fever primarily in the afternoons.

2.2 | Examination

Physical examination revealed hemodynamic stability (Blood pressure at 110/78 mmHg, heart rate at 60 beats per minute, respiratory rate at 18 cycles per minute, peripheral oxygen saturation at 98% on room air, pulse at 60 pulses per minute.), a mild fever at 38.3°C, and bilateral polyarthralgia involving the wrists, metacarpophalangeal, and proximal and distal interphalangeal joints. Additionally, a non-pruritic maculopapular rash on the trunk had appeared 2 weeks prior. A tumoral syndrome was noted, characterized by bilateral, painless, mobile axillary and cervical lymphadenopathy, the largest measuring 5 cm in its greatest dimension, along with stage 2 splenomegaly (Hackett's classification) and moderate hepatomegaly.

2.3 | Investigation

Laboratory tests revealed leukocytosis with a white blood cell count of 13.810/μL predominantly neutrophils,

TABLE 1 Summary of biological tests in our case.

Parameter	Value	Normal Value
White Blood Cells (/mm ³)	13,810	4000–10,000
Neutrophils (/mm ³)	8500	2000–7500
Lymphocytes (/mm ³)	1250	1000–4000
Hemoglobin level (g/dl)	11.1	12–16 (female)
Mean corpuscular volume (fl)	76	80–100
Platelets (/mm ³)	199,000	150,000–450,000
Creatinine (μmol/L)	67	44–110 (female)
C Reactive Protein (mg/L)	48	<6
Aspartate aminotransferase (IU/L)	26.7	10–40
Alanine aminotransferase (IU/L)	20.36	7–56
Lactate dehydrogenase (IU/L)	206	140–280
Creatinine phosphokinase (IU/L)	242	20–200
Glycolysed fraction of ferritin (%)	12	<10
Erythrocyte sedimentation rate (mm)	28	0–20 (female)
Serum ferritin (ng/ml)	3350	30–400
24-hour proteinuria (g/24h)	0.211	<0.15
Rheumatoid factors (IU/l)	<8	<14
Anti-citrullinated protein antibodies (IU/L)	<3.5	<20
Angiotensin converting enzyme (IU/L)	15	8–52
anti-ds-DNA antibody (UI/mL)	5	<20
Antinuclear antibodies (U)	0.1	≤1.0
Antinuclear Factors (U)	0.1	<1.0
Anti-neutrophil cytoplasmic antibody (AU/mL)	6	≤19
Anti-Ro (U)	0.1	<1.0

hyperferritinemia at 3550 ng/mL, and a glycosylated ferritin fraction of 12%. The biopsy of the accessory salivary glands with histological examination was normal. Further biological evaluations are summarized in Table 1.

2.4 | Diagnosis

Initial diagnosis considered was AOSD based on the Faustrel criteria (Table 2). An axillary lymph node biopsy presented as a cluster of micro-lymphadenopathies. A total of six lymph nodes were observed, measuring between 0.5 cm and 3 cm in their largest dimension. The nodes were grayish and had a soft consistency (Figure 1). No necrosis or hemorrhage was observed on the surface or

upon sectioning of the nodes. The histological immunohistochemical study identified a small B-cell non-Hodgkin lymphoma (NHL) grade I (Figure 2A). The immunohistochemical study identified positive staining with

anti-CD20, Bcl2, Bcl1, Bcl6, and CD10 antibodies. The Ki67 proliferation index was evaluated at 40% (Figure 2B). Consequently, a concurrent diagnosis of AOSD associated with small B-cell NHL was established.

TABLE 2 Faustrel criteria present in our patient.

Fautrel criteria	Present criteria
Major criteria	
Hectic fever $\geq 39^{\circ}\text{C}$	+
Arthralgia	+
Transient erythema	Absent
Pharyngitis	Absent
Neutrophil count $>80\%$	+
Glycosylated ferritin $\leq 20\%$	+
Minor criteria	
Maculopapular rash	+
Leukocyte count $>10,000/\text{mm}^3$	+

Note: The diagnosis is based on the presence of at least four major criteria or three major criteria combined with two minor criteria.



FIGURE 1 Left axillary adenopathy excision specimen.

2.5 | Treatment

The patient was treated with methylprednisolone at a dose of 32 mg per day, tapered by 10% every 10 days for AOSD and NHL, along with 4 courses of rituximab administered weekly for NHL.

2.6 | Outcomes

Clinical and biological improvement was observed, achieving remission within 6 months.

3 | DISCUSSION

AOSD pathogenesis lies at the intersection of inflammasomopathies and lymphohistiocytic activation.⁴ The diagnosis of AOSD is typically based on the classic triad of symptoms, including fever, polyarthralgia, and a transient rash. Despite this, it remains challenging due to the absence of specific tests and characteristic clinical manifestations, its low incidence, and the diversity of its clinical presentation. This disease primarily affects young adults, predominantly those aged 16 to 35, and is observed in both sexes without geographic distinction.⁴

The association between AOSD and neoplasms has been reported in a few cases, including cases of lymphomas. However, the simultaneous occurrence of these two pathologies is rarely described. This review of the literature on the simultaneous diagnosis of AOSD and lymphoma worldwide was conducted using the MEDLINE (via PUBMED) and Google Scholar databases. This research was supplemented by a manual search of the

FIGURE 2 (A) Histological examination of the ganlion shows a lymphoid proliferation of small cells, with cytonuclear atypia such as anisocytosis and anisokaryosis (G400). (B) Immunohistochemical image (Ki67 immunostaining, G400) showing intense nuclear labelling of tumor cells with some mitotic figures.

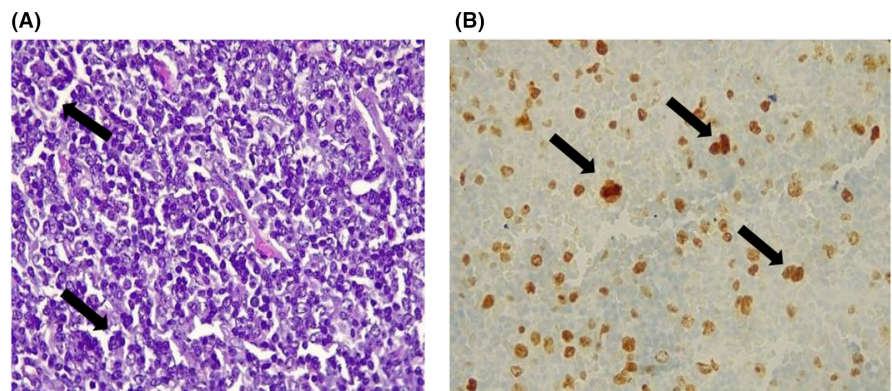


TABLE 3 Summary table of the different cases in our literature review.

N°	Authors/Year	Age/ Sex	Symptoms	Serum ferritin (ng/ml)/ Ferritin glycolytic fraction (%)	Type of lymphoma	Treatment by the AOSD	Treatment of lymphoma	Evolution
1	Isimbaldi et al/2000 ⁵	18 /M	Recurrent fever, skin rash and arthralgia	12,500/ on available	LMNH (angiotropic T)	Corticotherapy	Not available	Death due to multiple organ failure
2	Kato et al/2009 ⁶	25/M	Fever, sore throat, oligoarthralgia and skin lesions	727.4/ not available	LMNH (nasal NK)	Corticosteroid therapy	Chemotherapy	Not available
3	Bayala et al/2024	23/F	Recurrent fever and polyarthritits	3550/12	LMNH (small B cells)	Corticosteroid therapy	Chemotherapy	Complete remission of lymphoma, AOSD: controlled

Abbreviations: NHL, non-Hodgkin's lymphoma; NK, natural killer.

bibliographic references of all potentially eligible full-text articles. Publications were identified using the following keywords: "AOSD AND lymphoma AND association." We found two articles referenced in English, both of which were case reports where the diagnosis of AOSD and lymphoma was made simultaneously. Cases diagnosed post-mortem or during the course of the disease were excluded. Table 3 summarizes the different cases described in the literature as well as our case based on year, authors, age, sex of patients, type of lymphoma, treatments, and outcomes (Table 3).

The association of AOSD with other malignant pathologies remains controversial, but since the appearance of the Fautrel criteria in 2002, it is considered possible because these criteria give significant importance to serum ferritin and the glycosylated fraction of ferritin. The mechanisms underlying hyperferritinemia in AOSD are not fully understood. These ferritin levels are generally higher than those observed during inflammation and hepatic cytolysis.⁷ Some authors suggest an elevated ferritin level at 4 to 5 times the normal level with high sensitivity.² A very high ferritin level lacks specificity, whereas the drastically reduced glycosylated ferritin level is more specific, making it a major criterion for guiding the diagnosis.² When this criterion is considered, the diagnosis is retrospectively confirmed, especially in the absence of underlying infectious or neoplastic pathology.⁷ This score is useful for supporting the diagnosis in clinical practice, but the major criterion of glycosylated ferritin less than 20% is not pathognomonic for AOSD.

Hyperferritinemia is present in other pathologies such as cancers, chronic inflammatory rheumatism, and infections, but the decrease in the glycosylated fraction of ferritin is highly specific to AOSD. Indeed, several studies have examined the role of serum ferritin in lymphomas. For instance, Yoh et al. revealed that serum ferritin levels were significantly higher in patients with Hodgkin's lymphoma compared to controls. Thus, ferritin level appears to be a useful biomarker for the diagnosis and prognosis of lymphomas.⁸ However, in cases of AOSD, the peculiarity of hyperferritinemia is its elevation to five times the normal level, as in our case, where it was elevated to 12 times the normal level. In contrast, in our literature review, only the first patient had such an elevation of the ferritin level, being 41 times the normal level.

Regarding the glycosylated fraction of ferritin in lymphomas, studies have shown that it is elevated in patients with lymphomas and may correlate with the disease stage and treatment response.⁹ The exact mechanism by which the glycosylated fraction is elevated in lymphomas is not fully understood. However, it is believed to be related to the increased glucose metabolism in tumor cells.⁹ Tumor cells require large amounts of glucose to support their

growth and proliferation, and glycolysis is the primary metabolic pathway used to break down glucose.⁹ Thus, in our patient, the decrease in the glycosylated fraction of ferritin to 12% was not related to the lymphoma but rather suggested AOSD. It was one of our major criteria for diagnosing AOSD in our patient according to the Faustrel criteria. This measurement was not performed on the other two patients in our literature review because their diagnostic criterion was that of Yamaguchi.

The diagnosis of lymphoma was based on the biopsy and histological and immunohistochemical study of the lymph nodes in our case, as in other cases described in the literature. The lymphoma lesions in our case differed from those typically seen in AOSD, which are generally paracortical, mixed, diffuse, necrotic, or follicular.¹⁰ The follicular pattern is characterized by extensive hyperplasia of lymphoid follicles; the paracortical pattern by proliferation of paracortical zones; the diffuse pattern by diffuse hyperplasia of paracortical zones, without observation of lymphoid follicle structures; the necrotic pattern by proliferative expansion of paracortical zones, focal sparse necrosis, and nuclear fragmentation; and mixed patterns by lymphoid follicles or diffuse areas associated with paracortical zones.¹⁰

Some cases of the association between AOSD and lymphoma are described in the literature, in which AOSD precedes lymphoma or vice versa. Our case report is the first to describe a simultaneous diagnosis of AOSD and small B-cell type LMNH. It is the third such association reported in the literature. Remarkably, our patient achieved remission from both diseases. Notably, this is the first report of such an association in a black african individual. However, the diagnosis of these cases was made using Yamaguchi's diagnostic criteria, which raises the question whether these were pseudo-AOSD cases. Nonetheless, patients suffering from autoimmune diseases are more likely to develop lymphoma.¹¹ Particularly, Sjögren's syndrome appears to significantly increase the risk, with a prevalence of lymphoma up to 15 times higher.¹¹

For the treatment of AOSD, all three patients received corticosteroid therapy as symptomatic treatment. Certain biologics, such as anakinra and canakinumab, are indicated as maintenance therapy in cases of corticosteroid failure.¹² This highlights the importance of ruling out other differential diagnoses of AOSD, as some AOSD treatments can worsen the course of these differential diagnoses, particularly infectious diseases.

4 | CONCLUSION

The coexistence of AOSD and lymphoma poses significant diagnostic and therapeutic challenges. The immunopathological connections between AOSD and lymphoma

remain poorly understood, particularly given the extremely rare reported cases. Nevertheless, it is crucial to remain vigilant in the face of any anomalies in the clinical presentation of lymphoma or AOSD.

AUTHOR CONTRIBUTIONS

Yannick Laurent Tchenadoyo Bayala: Conceptualization; methodology; supervision; validation; visualization; writing – original draft. **Issa Ouedraogo:** Visualization; writing – original draft. **Hervé Eric Mourfou:** Visualization; writing – original draft. **Bakoubassé Aïssata Son:** Validation. **Wendyam Nadège Yameogo:** Validation. **AYOUBA TINNI Ismael:** Validation. **Joelle Wendlassida Stéphanie Zabsonre/ Tiendrebeogo:** Supervision. **Dieu-Donné Ouedraogo:** Supervision.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

I confirm that written patient consent has been signed and collected in accordance with the journal's patient consent policy, and that I have added a patient consent statement asserting this at the bottom of the manuscript's title page. I will retain the original written consent form and provide it to the Publisher if requested.

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