CASE REPORT

Association of systemic lupus erythematosus, Niemann-Pick disease type B, and probable granulomatosis with polyangiitis: A case report

Association d'un lupus érythémateux systémique, d'une maladie de Niemann-Pick de type B et d'une probable granulomatose avec polyangéite: A propos d'un cas

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Abstract

Introduction: Niemann-Pick disease type B (NPD B) is a rare autosomal recessive disorder. It is clinically characterized by hepatosplenomegaly, interstitial lung disease, and thrombocytopenia. Its clinical features may overlap with those of autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and Granulomatosis with Polyangiitis (GPA).

Observation: In this context, we report the first documented case of a 51-year-old woman presenting with the association of NPD B, SLE, and probable GPA. Clinically, the patient exhibited dyspnea, severe anemia, hepatosplenomegaly, Jaccoud's arthropathy, and crusted rhinitis. Laboratory tests were positive for antinuclear antibodies and anti-neutrophil cytoplasmic antigens. Radiological examinations showed interstitial pneumonia and pansinusitis. NPD B was suspected based on the presence of sea-blue histiocytes in bone marrow biopsy and confirmed by sphingomyelinase deficiency. After six months of corticosteroid and hydroxychloroquine therapy, the patient showed significant improvement.

Conclusion: This case highlights the importance of considering rare diseases in differential diagnosis, even when clinical signs suggest more common conditions.

Keywords: Autoimmunity, case report, metabolic diseases, sea-blue histiocyte syndrome

Résumé

Introduction: La Maladie de Niemann-Pick de type B (MNP B) est une maladie autosomique récessive rare. Elle se caractérise cliniquement par une hépatosplénomégalie, une pneumopathie interstitielle et une thrombocytopénie. Ses caractéristiques cliniques peuvent se chevaucher avec celles des maladies auto-immunes comme le Lupus Érythémateux Systémique (LES) et la Granulomatose avec Polyangéite (GPA).

Observation: Dans ce contexte, nous rapportons le premier cas documenté d'une femme âgée de 51 ans présentant l'association d'une MNP B, d'un LES et d'une probable GPA. Sur le plan clinique, la patiente présentait une dyspnée, une anémie sévère, une hépatosplénomégalie, une arthropathie de Jaccoud et une rhinite croûteuse. Les tests de laboratoire étaient positifs pour les anticorps antinucléaires et les antigènes cytoplasmiques anti-neutrophiles. Les examens radiologiques ont révélé une atteinte pulmonaire interstitielle et une pansinusite. La MNP B a été suspectée sur la base de la présence d'histiocytes bleu marins dans la biopsie de moelle osseuse et confirmée par le déficit en sphingomyélinase. Une évolution favorable a été observée après six mois de traitement par corticoïdes et hydroxychloroquine.

Conclusion: Ce cas souligne l'importance de penser à des pathologies rares dans le cadre du diagnostic différentiel même en présence des signes cliniques évoquant des maladies plus fréquentes.

Mots-clés : Auto-immunité, étude de cas, maladies métaboliques, syndrome des histiocytes bleus de mer

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Introduction

Niemann-Pick disease type B (NPD B) is a rare autosomal recessive disorder caused by an enzymatic deficiency of the enzyme sphingomyelinase, leading to sphingomyelin accumulation in lysosomes (1). This enzyme deficiency results in the accumulation of sphingomyelin in various organs, such as liver, spleen, and lungs (1). The accumulation of storage cells in the bone marrow may also lead to hematologic manifestations like anemia and thrombocytopenia (2). Some symptoms of this pathology may overlap with those observed in systemic diseases (3). Differential diagnoses include other lysosomal storage disorders, such as Gaucher and Fabry disease, and autoimmune diseases, such as sarcoidosis or mixed connective tissue disease (4). A careful, integrated diagnostic approach is essential for distinguishing between these overlapping conditions. The association of NPD B with autoimmune diseases is extremely rare, and only two cases of NPD B associated to Systemic Lupus Erythematosus (SLE) have been reported (3-4).
We presented the first documented case of NPD B associated with SLE and with probable Granulomatosis with Polyangiitis (GPA) in an adult.

Patient information

We described the case of a 51-year-old woman, with negative family history, admitted to the internal medicine department for progressive worsening dyspnea and severe anemia. She reported chronic pruritus and inflammatory arthralgia affecting both large and small joints.

Clinical findings

Physical examination revealed a thin patient with a low body mass index at 17 kg/m². Pulmonary auscultation detected crackles and abdominal examination showed hepatosplenomegaly. Reducible joint deformities in the hands resembling Jaccoud's arthropathy were noted (Figure 1). Additionally, the patient presented with vascular purpura, ichthyosis, and crusted ulcerated rhinitis.

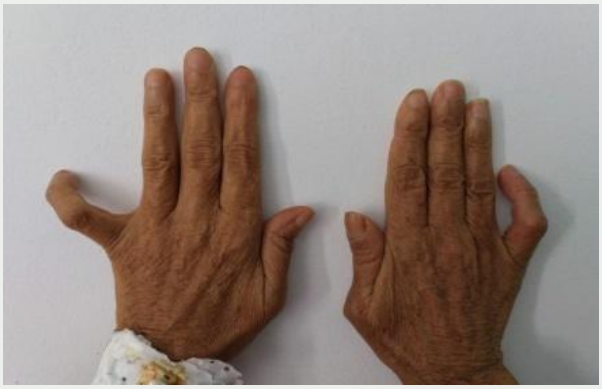

Figure 1. Joint deformities 'Jaccoud arthropathy'

Timeline

Table 1 presents the medical history timeline.

Table 1. Medical history timeline

Time	Symptoms/diagnostic	Treatment/action
10.02.2024	hypoxemic pneumonia	oxygen therapy (pulmonary department)
20.04.2024	severe anemia	blood transfusion (hematology department)
12.09.2024	worsening dyspnea, inflammatory arthralgia and bicytopenia	admission to the internal medicine department

Diagnostic assessment

Laboratory investigations identified severe anemia (Hemoglobin = 7 g/dl, normal range: 12 to 16 g/dL), thrombocytopenia (platelet count = 70000/ mm³, normal range: 150 000 to 400 000/mm³), an elevated erythrocyte sedimentation rate (ESR) of 120 mm/h (normal range: < 30 mm/h), and 24-hour protein excretion of 2g (normal range: < 0.15 g/24). The patient also had hypercholesterolemia (6.2 mmol/L, normal range: < 5.2 mmol/L) and elevated triglyceride levels (3.4 mmol/L, normal range: < 1.7 mmol/L). At this stage, several differential diagnoses were considered due to the constellation of hematological abnormalities, proteinuria, dyslipidemia, and systemic inflammation. Hematological malignancies were suspected due to the presence of cytopenias and the potential involvement of the bone marrow. Autoimmune diseases, such as SLE and sarcoidosis, were suspected as well, particularly given the systemic inflammatory profile and multiorgan involvement.
To further explore the autoimmune hypothesis, an immunological evaluation was carried out. Coombs' tests were negative, and complement levels were within normal limits (C3: 0.99 g/L, normal range: 0.9-1.8 g/L; C4: 0.34 g/L, normal range: 0.1-0.4 g/L). However, autoimmune screening revealed positive antinuclear antibodies (ANA= 1/400), including native anti-DNA and anti-Sm antibodies, as well as positive antineutrophil cytoplasmic antibodies (ANCA) type PR3-ANCA.
A thoracic computed tomography (CT) scan, conducted due to the patient's dyspnea, showed multiple mediastinal lymphadenopathies and a typical usual interstitial pneumonia pattern. Given these findings, in association with positive PR3-ANCA and a history of chronic sinusitis, a CT scan of the sinuses was performed. It demonstrated a deviation of the nasal septum along with pansinusitis.
The diagnosis of SLE was established according to the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria (5), which integrate both clinical and immunological findings. Key diagnostic features included hematologic abnormalities (anemia with hemoglobin levels below 10 g/dL and thrombocytopenia with platelet counts under 100,000/mm³), vascular manifestations such as purpura, and reducible joint deformities. Immunological

confirmation was achieved through the presence of anti-DNA and anti-Sm antibodies, collectively yielding a weighted score surpassing the 10-point diagnostic threshold.

The patient's presentation of crusted rhinitis, pansinusitis, and PR3-ANCA positivity strongly suggested GPA. This clinical and serological profile yielded a diagnostic score of 9 points, comfortably exceeding the 5-point threshold required for diagnosis according to the 2022 ACR/EULAR classification criteria (6).

Therapeutic intervention

The patient received three days of methylprednisolone at a dose of 15 mg/kg/day, followed by 1 mg/kg/day of prednisone for six weeks with a gradual taper, in combination with hydroxychloroquine. Cyclophosphamide courses were administered at weeks 0, 2, and 4, then every three weeks for six months, followed by a switch to azathioprine.

Follow-up and outcomes

Due to persistent non-immunological anemia and thrombocytopenia, a bone marrow biopsy was performed. It revealed normal hematopoietic lineages with a macrophagic infiltrate suggestive of sea-blue histiocyte disease (Figure 2). Given the presence of pulmonary involvement and hepatosplenomegaly, NPD B was the main suspected diagnosis. Sphingomyelinase activity was therefore measured and found to be deficient. Molecular analysis, performed after obtaining informed consent and providing genetic counseling, revealed the presence of the c.1829_1831del mutation (p.Arg610del). Unfortunately, the patient could not receive enzyme substitution therapy due to financial constraints. However, the patient has not experienced any flare-ups or episodes of hypoxaemic pulmonary infections after six months of corticosteroid, cyclophosphamide and hydroxychloroquine therapy.

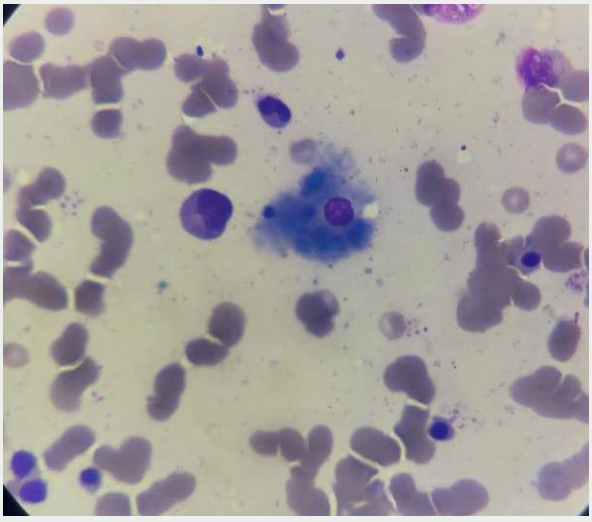

Figure 2. Microscopic appearance of the patient's bone marrow showing sea-blue histiocyte with eccentrically displaced nuclei and cytoplasm packed with blue-green granules, characteristic of NPD

Discussion

To the best of the authors' knowledge, this is the first reported case of the association between NPD B, SLE, and probable GPA. This exceptional combination raises the possibility of shared immunopathogenic pathways between lysosomal storage disorders and systemic autoimmune diseases.

NPD B is an autosomal recessive lysosomal storage disorder caused by mutations in the sphingomyelin phosphodiesterase 1 gene, leading to acid sphingomyelinase deficiency (1). This deficiency results in the accumulation of sphingomyelin in various organs, particularly the liver and spleen, causing hepatosplenomegaly, which is a hallmark of the disease (1). Unlike type A, NPD B does not present with neurological involvement, allowing patients to survive into adulthood, albeit with chronic complications such as respiratory issues and liver dysfunction (2).

The coexistence of NPD B with autoimmune diseases such as SLE is exceptionally rare, with only two cases reported in the literature (3-4). This scenario presents a dual diagnostic challenge for clinicians. First, it requires identifying a storage disorder in a patient presenting with clinical and laboratory features suggestive of autoimmunity. Several studies have reported that patients with lysosomal storage disorders may develop non-specific and possibly non-pathogenic autoantibodies (7-8). This may result from chronic immune system stimulation caused by the intracellular accumulation of storage materials (9). In NPD B, the buildup of sphingomyelin impairs normal cellular function and may trigger immune activation pathways (7). Such dysregulation might explain why some individuals exhibit features of SLE or other autoimmune diseases in parallel with their underlying metabolic disorders (10). In these cases, the clinician will face a significant challenge with overlapping clinical presentations. The second challenge lays in the management of these patients, who require immunosuppressive treatment, which can lead to pulmonary infections, a major complication in NPD B (7). In addition, the unavailability of enzyme substitute therapy in some regions complicates disease management.

The principal limitation of this case is the absence of histological confirmation. However, based on clinical and biological criteria, and taking into account the positivity of PR3-ANCA, the diagnosis of GPA is highly probable. In this patient, bronchoscopy to assess for alveolar hemorrhage was deferred due to hematologic instability and the absence of hemoptysis. A biopsy of the cutaneous purpuric lesions was not performed, as the lesions were no longer active and had nearly resolved at the time of evaluation. Certainly, histological verification would have been particularly valuable in this first reported association of SLE, GPA and NPD B. However, these procedures may carry disproportionate risks in fragile patient.

In conclusion, given the chronic nature of autoimmune diseases and lysosomal storage disorders, a multidisciplinary approach involving rheumatologists,

geneticists and other specialists is essential to ensure optimal patient management. Regular monitoring of the complications associated with each pathology is crucial, including pulmonary function tests for respiratory impairment and screening for thrombotic events.

Patient perspective

The patient experienced a significant improvement in joint pain, ichthyosis, and chronic pruritus, leading to an improved quality of life.

Informed consent

Written informed consent was obtained from the patient to publish this case report.

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