Clinical Case Report

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Anti-NXP2-antibody-positive immune-mediated necrotizing myopathy associated with acute myeloid leukemia

A case report

Lina Su, MMed[a], Yue Yang, MD[a,*], Yuan Jia, MD[a], Xu Liu, MD[a], Wei Zhang, MD[b], Yun Yuan, MD[b], Zhanguo Li, MD, PhD[a]

Abstract

Rationale: Idiopathic inflammatory myopathies have been extensively reported associated with malignancy. Immune-mediated necrotizing myopathy (IMNM), however, has rarely been connected with malignancy including acute myeloid leukemia (AML).

Patient concerns: A 65-year-old woman was diagnosed with AML and received regular chemotherapy. After the 5th cycle chemotherapy, she achieved complete remission but developed severe muscle weakness and myalgia with dramatic increasing creatine kinase (CK).

Diagnosis: The positivity of antinuclear matrix protein 2 antibody (anti-NXP2 Ab) and muscle biopsy in together confirmed the diagnosis of IMNM.

Intervention: Methylprednisolone and intravenous immunoglobulin was administered.

Outcomes: This treatment resulted in a dramatic clinical and laboratory improvement within 1 month. CK and lactate dehydrogenase levels dropped sharply to normal. Anti-NXP2 Ab was shown to disappear in a repeated test afterwards.

Lessons: The IMNM is also closely related to malignancy. We here report a case of IMNM associated with AML for the first time. Anti-NXP2 Ab may be utilized as both diagnostic and prognostic markers of paraneoplastic IMNMs.

Abbreviations: AML = acute myeloid leukemia, anti-NXP2 Ab = antinuclear matrix protein 2 antibody, DM = dermatomyositis, IIMs = idiopathic inflammatory myopathies, IMNM = immune-mediated necrotizing myopathy, MSAs = myositis-specific autoantibodies, PM = polymyositis.

Keywords: acute myeloid leukemia, anti-NXP2 Ab, Immune-mediated necrotizing myopathy

1. Introduction

Immune-mediated necrotizing myopathy (IMNM) is a recently identified subgroup of idiopathic inflammatory myopathies (IIMs). Distinguished from polymyositis (PM) and dermatomyositis (DM), IMNM features widespread myofiber necrosis and regeneration with the absence of inflammatory cell infiltrates on muscle biopsy. Although the association between PM/DM and malignancy has been extensively reported and several myositis-specific autoantibodies (MSAs) including antinuclear matrix protein 2 antibody (anti-NXP2 Ab) have been recognized as predictors in this setting,[1] paraneoplastic IMNM is considered a relatively rare clinical entity. In this report, we describe the first case of acute myeloid leukemia (AML)-associated IMNM positive for anti-NXP2 Ab.

2. Clinical report

A 65-year-old woman presented with fatigue in June 2016. On admission, physical examination showed mild pallor. No jaundice, edema, purpura, petechiae, or ecchymosis was noted. Neurologic examination and muscle strength were normal. Laboratory data showed a white blood cell count of 2.21×10^9/L, hemoglobin 90 g/L, and platelet count 255×10^9/L. Serum biochemical parameters including creatine kinase (CK) were within the normal range. Bone marrow aspiration showed a hypercellular marrow with 40% myeloblast, which presented with cytochemical statins for peroxidase, nonspecific esterase, and sodium fluoride. Cytogenetic analysis revealed a normal karyotype. Reverse transcription-polymerase chain reaction analysis demonstrated the presence of Nucleophosmin 1 and Wilm's tumor suppressor gene1-mutated gene. The diagnosis of AML of French-American-British subtype M2 was established. Chemotherapy with mitoxantrone and cytarabine regimen was started. Complete remission was achieved 1 month later.

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This study was approved by the Research Ethics Committees of Peking University People's Hospital. Written informed consent was given by the patient.

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[a] Department of Rheumatology and Immunology, Peking University People's Hospital, [b] Department of Neurology, Peking University First Hospital, Beijing, China.

[*] Correspondence: Yue Yang, Department of Rheumatology and Immunology, Peking University People's Hospital, 11 Xizhimen South St, Beijing 100044, China (e-mail: yyang216@icloud.com).

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Sequential chemotherapy with 1 course of standard-dose cytarabine followed by 3 cycles of high-dose cytarabine was administered subsequently every one and a half months. One month after her 5th course of cytarabine chemotherapy, the patient complained of muscle weakness and myalgia, which rapidly developed into disability to walk or even sit up by herself within 10 days. No change in urine volume or color was seen.

2.1. Physical examination and diagnostic assessment

Physical examination disclosed severe symmetrical weakness of her neck, shoulder girdle and pelvic girdle muscles (MRC grade 3). There was prominent tenderness on proximal muscles. Deep tendon reflex was slightly decreased but no sensory disturbance or muscle atrophy was observed. No rash was noticed. Repeated complete blood cell count and bone marrow aspiration were uneventful. Urine analysis was positive for occult blood and negative for protein. Serum biochemistry test revealed a dramatic increase of CK (13,300 U/L), myoglobin (1560 ng/mL), and lactate dehydrogenase (777 U/L) levels.

Considering the patient's history of previous administration of cytarabine, drug-induced rhabdomyolysis was considered at first. Rhabdomyolysis has been previously reported as a complication of cytarabine-containing regimens in a few cases, wherein muscle damage all appeared within 3 days after the first dose.[2] In the present study, however, the patient's symptoms did not appear until the 5th course. After vigorous hydration with isotonic saline, followed by alkaline solutions and mannitol, the patient showed no improvement in muscle weakness. Instead, her condition deteriorated and CK level increased to 16,000 U/L. Since the treatment response did not support the diagnosis of drug-induced rhabdomyolysis, further investigations including autoantibodies were conducted, which showed positive for anti-NXP2 Ab and negative for antinuclear Ab, myositis-associated antibodies, and other MSAs. Electromyography indicated myogenic injury. Muscle biopsy confirmed the presence of myofiber necrosis and regeneration, combined with a mild lymphocytic infiltrate (Fig. 1). Thus, the diagnosis of IMNM was made.

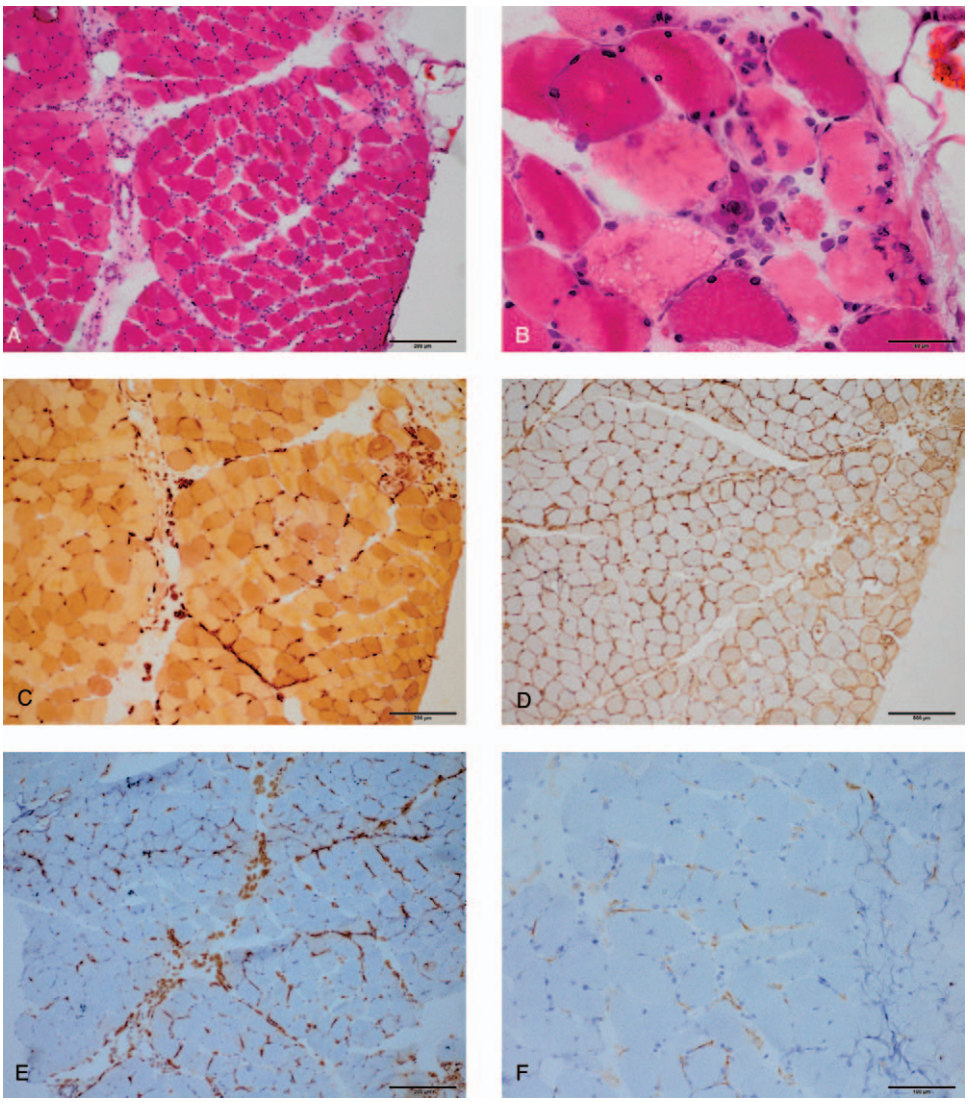

Figure 1. Muscle biopsy pattern of the left biceps brachii. Hemotoxylin and eosin staining illustrates necrotic and regenerating fibers with a localized distribution (A, B), while nonspecific esterase highlights myophagocytosis (C). MHC class I is expressed on the sarcolemma of numerous myofibers with weak intensity (D). CD68-positive macrophages can be identified in the fibers undergoing myophagocytosis (E) and CD8-positive lymphocytes are occasionally detected endomysially (F).

2.2. Therapeutic intervention

Accordingly, treatment was begun with methylprednisolone 0.8 mg/kg/d and intravenous immunoglobulin 20 g for 5 days.

3. Results

The treatment resulted in a dramatic clinical and laboratory improvement within 1 month. CK and lactate dehydrogenase levels dropped sharply to normal. Anti-NXP2 Ab was shown to disappear in a repeated test afterwards.

4. Discussion

Neoplasm can be diagnosed before, concurrent with, or after the diagnosis of IIM. Unlikely PM/DM, IMNM was seldom investigated for its association with malignancy. Not until recently did some studies find the relevance between IMNM and gastrointestinal tumors, small cell lung cancer, or breast cancer.[3] IIM associated with AML has rarely been described. There have been only 8 patients diagnosed with AML-associated PM/DM till date. In all the cases, AML appeared concurrently with or after the onset of PM/DM.[4,5] We here for the first time report a patient who developed IIM,- IMNM to be specific, after having achieved complete remission of AML. This may raise a suspicion: is this a real consequence, or just a coincidence? Although the pathogenesis of paraneoplastic myopathy remains enigmatic, shared-epitope theory was recognized as one possible mechanism. In patients with malignancy, mutated self-proteins could become the target of an antitumor response, led to the emergence of antibodies against myositis autoantigens expressing shared epitopes with these proteins. After a second "hit," this immune response could cause the occurrence of myositis, even after the elimination of malignancy.[6] Therefore, we speculate the development of IMNM was most likely the consequence of AML.

It is noteworthy that anti-NXP2 Ab was positive during active myositis and disappeared after disease remission of IMNM. Initially viewed as a major MSA in Juvenile Dermatomyositis with predictive value of severe disease, subcutaneous calcinosis, and muscle contractures, anti-NXP2 Ab was reported in patients with PM/DM associated with malignancy afterwards.[7]Currently, it has been recognized as an MSA firmly related to paraneoplastic myopathy. Although it has not been reported in patients with anti-NXP2 Ab, negativation or decrease in titers of anti-MDA5, anti-SRP, and anti-HMGCR Abs were observed in correlation with clinical improvements in earlier studies on patients with IIM.[8] It is therefore feasible that anti-NXP2 Ab could also be utilized as both diagnostic and prognostic markers of disease.

Author contributions

Conceptualization: Yue Yang.
Investigation: Lina Su, Yue Yang, Yuan Jia, Xu Liu, Wei Zhang.
Project administration: Yue Yang.
Supervision: Yue Yang, Zhanguo Li.
Validation: Yuan Jia, Wei Zhang, Yun Yuan.
Writing – original draft: Lina Su.
Writing – review & editing: Yue Yang.

References

[1] Aggarwal R, Oddis CV. Paraneoplastic myalgias and myositis. Rheum Dis Clin North Am 2011;37:607–21.
[2] Truica CI, Frankel SR. Acute rhabdomyolysis as a complication of cytarabine chemotherapy for acute myeloid leukemia: case report and review of literature. Am J Hematol 2002;70:320–3.
[3] Wegener S, Bremer J, Komminoth P, et al. Paraneoplastic necrotizing myopathy with a mild inflammatory component: a case report and review of the literature. Case Rep Oncol 2010;3:88–92.
[4] Shen JK, Ding YM, Zhou WJ, et al. Polymyositis/dermatomyositis associated with acute myelocytic leukemia. Rheumatol Int 2008;28: 1265–7.
[5] Shrivastav A, Kumar V, Pal J. Dermatomyositis associated with acute myelocytic leukemia. Rheumatol Int 2010;30:671–3.
[6] Joseph CG, Darrah E, Shah AA, et al. Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 2014;343:152–7.
[7] Ichimura Y, Matsushita T, Hamaguchi Y, et al. Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy. Ann Rheum Dis 2012;71:710–3.
[8] Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. J Intern Med 2016;280:8–23.