Microscopic Polyangiitis with Pulmonary-renal Involvement in a Patient with Polyarticular Juvenile Idiopathic Arthritis: A Case Report

Abstract

The association of polyarticular juvenile idiopathic arthritis (p-JIA) and microscopic polyangiitis (MPA) is extremely rare. Very few case reports described the coexistence of these two diseases to date. Here we report a 26-year-old female, a diagnosed patient of rheumatoid factor positive p-JIA for 15 years who developed MPA with renal and pulmonary involvement at the age of 26 years. She was successfully treated with intravenous corticosteroid and injection rituximab. This case report is unique as an association between MPA and p-JIA is very rare.

Keywords: *Microscopic polyangiitis, polyarticular juvenile idiopathic arthritis, pulmonary, renal*

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises three clinical entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). MPA is a systemic necrotising vasculitis that affects small-caliber vessels (capillaries, venules, and arterioles). Its clinical manifestations are to some extent similar to those of polyarteritis nodosa (PAN), but it is characterized by the presence of rapidly progressive glomerulonephritis and pulmonary capillaritis, which are normally not seen in PAN.

Juvenile idiopathic arthritis (JIA) is arthritis of unknown etiology that begins before the age of 16 years and persists for at least 6 weeks. According to the International League of Associations for Rheumatology classification criteria, polyarticular JIA (p-JIA) is defined as the involvement of five or more joints during the first 6 months of disease onset. The subgroup of p-JIA with a positive rheumatoid factor (RF) for at least two occasions at an interval of 3 months is termed as RF positive p-JIA.[1] p-JIA is characterized by symmetric involvement of joints. Concomitant presence of p-JIA and MPA is extremely rare and to the best of our knowledge, only two such cases have been described in the literature.[2]

Herein, we present the case report of a 26-year-old young lady who was diagnosed as RF-positive p-JIA at the age of 11 years and developed MPA with renal and pulmonary involvement currently. She was managed successfully with corticosteroid and rituximab.

Case Report

A 26-year-old lady, diagnosed patient of RF positive p-JIA, presented to the Rheumatology outpatient clinic with a history of gradually progressive fatigue, lethargy, and a decrease in urine volume for the last 4 months. She developed inflammatory polyarthritis at the age of 11 years involving small and large joints of all limbs. She did not have any history of fever, oral ulcers, alopecia, malar rash, or photosensitivity. Her rheumatoid factor was positive [122 IU/ml (cutoff <10.4 IU/ml)]. She was diagnosed as p-JIA and treated with tablet methotrexate, sulfasalazine, and on-demand NSAIDs.

During the current visit, her serial laboratory parameters showed gradual decrease in hemoglobin (9 gm/dL→3.9 gm/dL) and rise in serum creatinine level (1 mg/dL→2.9 mg/dL) over 4 months. She did not give a history of bleeding. She was

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How to cite this article: Kumar MS, Mondal S, Sircar G, Ghorai S, Haldar S, Ghosh A. Microscopic polyangiitis with pulmonary-renal involvement in a patient with polyarticular juvenile idiopathic arthritis: A case report. Indian J Nephrol 2023;33:132-5.

Received: 27-09-2021
Revised: 27-10-2021
Accepted: 03-12-2021
Published: 08-08-2022

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Access this article online

Website: https://journals.lww.com/ijon

DOI: 10.4103/ijn.ijn_414_21

Quick Response Code:

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admitted for further evaluation and management. On examination, she had pallor, tachycardia (pulse rate: 110/min, regular), and high blood pressure (150/90 mm Hg). Joint examination showed tender joint count- 0/28, swollen joint count- 0/28, flexion deformities in bilateral wrist joints and left elbow joint, and boutonniere deformity of the left ring finger, left little finger, and right ring finger. The probable etiologies of her severe anemia and worsening creatinine values were kept as NSAID-induced nephropathy with occult gastrointestinal blood loss, membranous nephropathy, and systemic small-vessel vasculitis.

In-hospital investigations showed hemoglobin-3.9 gm/dl, total leukocyte count- 6240/µL (normal range: 4000–11 000/µL), platelet count- 3.3 lakhs/ml (normal range: 150 000–400 000/mL), serum urea- 63 mg/dl, creatinine-2.3 mg/dl, normal liver function test, and electrolytes levels. Peripheral blood smear showed a microcytic hypochromic picture, serum iron was 64 mcg/dL, high total iron-binding capacity (426 mcg/dl), low transferrin saturation (14.29%), and serum ferritin level was 86.7 µg/L. Her direct Coomb's test was negative. She was transfused with five units of packed red blood cells and her hemoglobin level increased to 8.9 gm/dl. Her urine microscopic examination showed albumin- 3+, RBC- 4–6/hpf, WBC- 6–8/hpf, and her 24-h urine protein excretion was 3.6 gm. Her immunological workup showed positive RF (218 IU/ml; cutoff: <10.4 IU/ml) and anti-cyclic citrullinated peptide antibody (195 RU/ml; cutoff: 5 RU/ml). Indirect immunofluorescence showed p-ANCA positivity (intensity: 3+), and myeloperoxidase (MPO) titer by ELISA was significantly raised (274 RU/ml; cutoff: 2 RU/ml). Her ANA was negative. Complement (C) 3 level was 37.8 mg/dl (normal: 90–180 mg/dl) and C4 level was 13 mg/dl (normal: 10–40 mg/dl). X-ray of both wrist and hand joints showed bilateral carpal bone erosions and fusions [Figure 1]. Upper GI endoscopy showed non-bleeding gastric ulcer. Her renal biopsy was suggestive of pauci-immune crescentic glomerulonephritis [Figure 2]. During in-hospital, she developed acute-onset cough and expectoration of bloody sputum. There was no associated fever and breathlessness. Blood investigations showed a drop in hemoglobin level (8.9 gm/dL→6.6 gm/dL). High resolution computed tomography of the chest showed patchy opacities in bilateral lower lobes. Bronchoalveolar lavage showed hemorrhagic fluid with alveolar macrophages; gram stain and cultures were sterile, suggestive of diffuse alveolar hemorrhage (DAH). She was diagnosed as having MPA with renal and pulmonary involvement with coexistent p-JIA. She was treated with a pulsed dose of intravenous methylprednisolone 500 mg daily for 3 days, followed by oral prednisolone 1 mg/kg/day, and intravenous rituximab (500 mg on day 0 and day 14) for remission induction.

After treatment, she showed improved renal function and chest symptoms. Her investigations after 1 month follow-up were: hemoglobin- 9.8 gm/dL, total leukocyte count- 9000/µL (normal range: 4000–11 000/µL), platelet count- 3.1 lakhs/ml (normal range: 150 000–400 000/mL), serum urea- 47 mg/dl, and creatinine- 1.7 mg/dl.

Discussion

RF-positive p-JIA tends to affect older children, with the onset of the disease typically occurring between 10 and 13 years of age. There is a much higher preponderance of females affected with RF-positive disease outnumbering their male counterparts by a ratio of 8–9:1.[3] The development of p-JIA is mostly indolent, with symmetric involvement of joints. Older children tend to have more severe disease, mimicking their adult counterparts with RA. Our patient developed p-JIA at the age of 11 years with an indolent disease course and symmetrical involvement of joints with strongly positive rheumatoid factor. Later, she gradually developed deformities of fingers. Diagnosis is p-JIA is mainly based on clinical findings. Laboratory findings observed are anemia, elevated acute phase

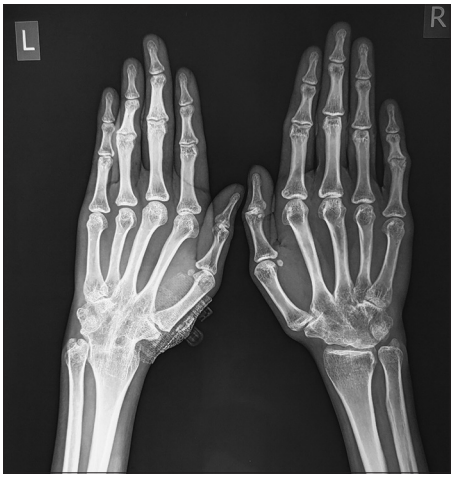

Figure 1: X-ray of both hands showing bilateral carpal bone erosions and fusions

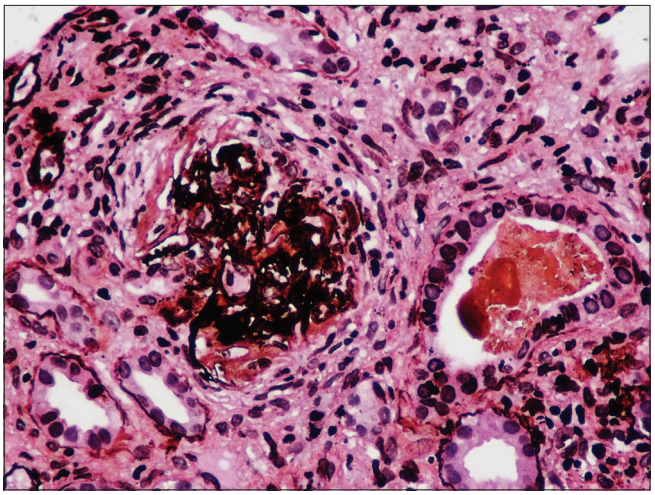

Figure 2: Renal biopsy showing crescentic glomerulonephritis

reactants, and RF positivity. Treatment is targeted toward achieving remission and preventing complications. Treatment options include NSAIDs, conventional disease modifying antirheumatic drugs, (DMARDs), and biologic DMARDs.

MPA was classified by the revised international Chapel–Hill Consensus Conference, 2012 as necrotizing small-vessel vasculitis (SVV), with little or no immune-complex deposition.[4] MPA primarily affects the kidneys and lungs. The prevalence of MPA ranges from 9 to 94 cases per million persons.[5] Its incidence increases with age.[6] Patients often present with non-specific complaints such as cough, dyspnea, and hemoptysis. The typical presentation of renal involvement is that of rapidly progressive glomerulonephritis as seen in our patient. The most common respiratory tract symptoms in MPA are cough, hemoptysis, dyspnea, and pleuritic pain. The severity of symptoms and signs varies from asymptomatic to acute and fulminant alveolar hemorrhage with respiratory failure. Fibrosing ILD is also noted in patients with MPA.[7] Testing for ANCA should be done in patients presenting with symptoms suggestive of AAV. CT scan should be performed in all patients having respiratory symptoms. Whenever possible, the diagnosis of MPA should be confirmed by biopsy of a site of suspected active disease. Granulomas are typically absent in biopsy specimens with pauci-immune deposits. Treatment has two main components: induction and maintenance. For life-threatening or organ-threatening diseases, induction with glucocorticoids with rituximab or cyclophosphamide is recommended. Rituximab, azathioprine, and mycophenolate are preferred agents for maintenance therapy. Survival at 5 years is 74%, and death takes place due to alveolar hemorrhage, digestive, kidney, and heart disorders.[5]

Our patient developed deranged renal function and DAH after 15 years of primary diagnosis of p-JIA. Her MPO levels were markedly elevated, and p-ANCA was positive. She had p-JIA with MPA overlap syndrome. To the best of our knowledge, only two cases of coexistent MPA and p-JIA were published previously.[2] The first case was a 23-year-old female, diagnosed to have MPA at the age of 10. Arthritis occurred 16 months later, and she was diagnosed with p-JIA. Initially, she achieved remission for MPA with methylprednisolone pulse and cyclophosphamide. For p-JIA, methotrexate was added and arthritis was resolved. The second case was a 14-year-old female who developed arthritis at the age of 11. She was diagnosed as having p-JIA and treated with prednisolone, methotrexate, and etanercept. She presented with hematuria and proteinuria at the age of 14 and was diagnosed with MPA. Her symptoms ameliorated with a combination of methylprednisolone pulse and rituximab. Similarly, our case also developed arthritis initially followed by renal involvement and DAH after 15 years.

Neutrophil extracellular traps (NETs) are operative in the pathogenesis of AAV. One recent study has shown that the disease status of RA is associated with increased NETosis, and RA patients exhibited significantly higher levels of MPO-DNA complexes.[8] Interestingly, peptidyl arginine deiminase type 4 (PADI4) gene polymorphism is associated with anti-CCP autoantibody positivity in JIA. PADI4 can enter the nucleus of neutrophils and causes histone citrullination, and histone citrullination can cause NETosis.[9] However, these are discrete observations, and any common pathogenic mechanism responsible for the development of these two diseases is yet to be established strongly.

Treatment should be chosen to manage both conditions. The agents most frequently used are corticosteroids and other DMARDs. Rituximab is often used for severe polyarticular JIA and was approved for the treatment of patients with AAV. Our patient was given methylprednisolone pulse therapy, followed by oral corticosteroid. Rituximab was considered as a second immunosuppressive induction agent as this agent is effective for the management of both the MPA and p-JIA. After treatment, our patient showed improved renal function and chest symptoms.

This case illustrates the unusual coexistence of two different autoimmune diseases in a patient. AAV should be considered as an important differential in any patient with rapidly developing pulmonary-renal syndrome.

Consent to publish statement

Written, informed consent was obtained from the patient for the publication of this case report.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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