# Uncommon onset manifestations without renal involvement in microscopic polyangiitis: A case report

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Received May 3, 2022; Accepted September 2, 2022

DOI: 10.3892/etm.2022.11668

**Abstract.** Microscopic polyangiitis (MPA) is a rare, idiopathic, autoimmune, systemic disease that most frequently involves the kidneys. The present study reports the case of a 48-year-old female patient who presented with diffuse myalgia, arthralgia of both hands and feet for 2 weeks before being admitted to the hospital. The patient exhibited involuntary loss of weight and occasional slight fever. Physical examination noted microstomia and perioral radial furrows, slight skin induration of the hands, discrete cyanotic skin areas on the dorsal side of both feet. The patient also presented bilateral crepitant rales. Laboratory findings at admission revealed non-specific biological inflammatory syndrome consisting of high erythrocyte sedimentation rate and high C-reactive protein. The patient was initially suspected of systemic sclerosis due to the appearance of microstomia and the slight skin induration of the hands with diffuse arthralgia and myalgia, although with negative immune tests (anti-SCL70 and anti-centromere B antibodies) and normal nailfold capillaroscopy. Instead, a high titer of MPO-ANCA was detected. The computerized tomography scan revealed early diffuse interstitial lung disease (ILD). Cases of MPA with pulmonary involvement, such as ILD before the onset of vasculitis or kidney involvement, are known. Therefore, the diagnosis of MPA was formulated considering the symptoms, the clinical examination and the high titer of MPO-ANCA. The particularity of the present case consists in the uncommon onset with atypical skin changes, positivity to MPO-ANCA, absent renal dysfunction and ILD involvement.

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*Abbreviations:* ANCA, antineutrophil cytoplasmic autoantibodies; AAV, ANCA-associated vasculitis; c-ANCA, cytoplasmic ANCA; p-ANCA, perinuclear ANCA; CHCC, Chapel Hill Consensus Conference; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; ILD, interstitial lung disease; IBD, inflammatory bowel disease; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO-ANCA, ANCA against myeloperoxidase; PAN, polyarteritis nodosa; PF, pulmonary fibrosis; PR3-ANCA, ANCA against proteinase 3; SLE, systemic lupus erythematosus

*Key words:* microscopic polyangiitis, antineutrophil cytoplasmic autoantibodies, ANCA-associated vasculitis, MPO-ANCA, diffuse interstitial lung disease

## Introduction

Microscopic polyangiitis (MPA) is a rare, idiopathic, autoimmune, systemic disease, and it is classified as antineutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis (AAV) (1). It is defined as a necrotizing vasculitis, with few or no immune deposits. It predominantly affects small blood vessels (capillaries, venules, arterioles and small arteries) and medium arteries, while it does not involve granulomatous inflammation (1). This disease is associated with the presence of ANCA, which are predominantly directed against myeloperoxidase (MPO-ANCA), and in a minority of patients directed against proteinase 3 (PR3-ANCA) (1). Other types of AAV include granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) (1). The worldwide annual cumulative incidence of MPA (new cases) is estimated to be 3-24 per million inhabitants, with a prevalence of 25-94 per million inhabitants (new and pre-existing cases). It affects all ethnical groups with a predominance in Caucasian individuals (2-4). Men seem to be slightly more frequently affected by this disease than women (2-4). The age at the onset of the symptoms is estimated to be around 50 years. MPA is more common in the south of Europe, while GPA is more common in the north (2-4).

Although it is considered that MPA most frequently involves the kidneys (5), the lung involvement is another important feature of MPA. The current study reports a case of MPA with PF.

## Case report

The present study reports the case of a 48-year-old woman who was admitted in Center of Rheumatic Diseases (Bucharest, Romania) complaining of diffuse myalgia and arthralgia of

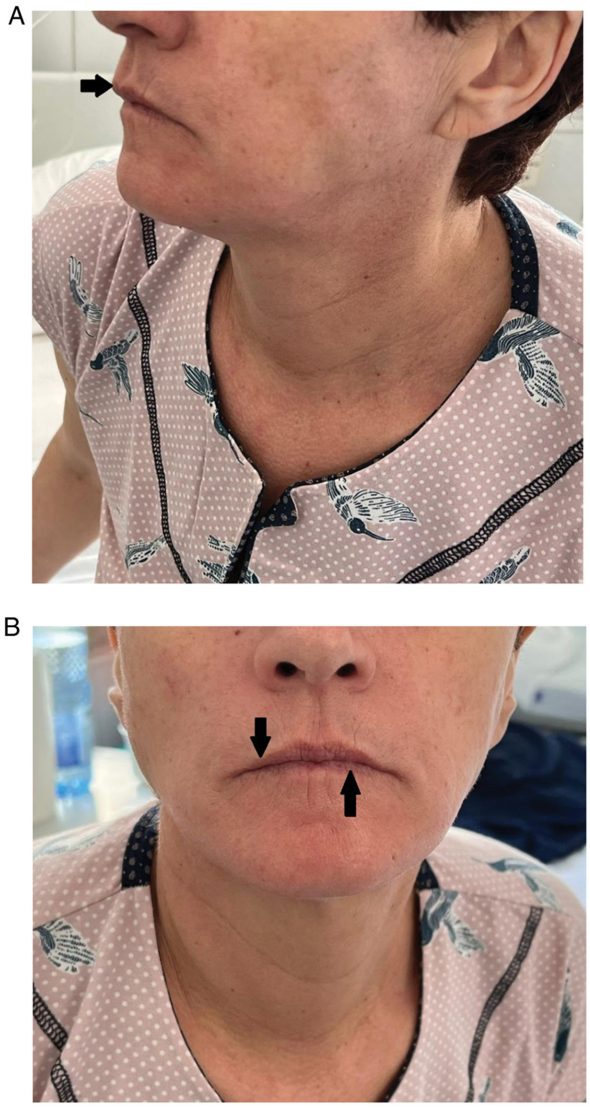


Figure 1. (A) Microstomia and (B) perioral radial furrows (black arrows).

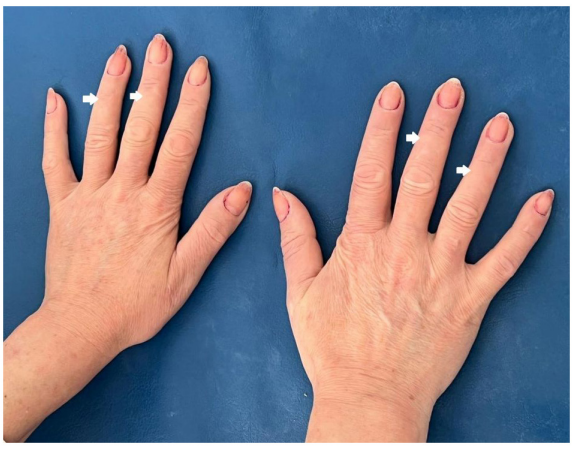

Figure 2. Slight skin induration of the hands (white arrows).

both hands and feet. The patient also described involuntary loss of weight and occasional slight fever. The patient had family history of colorectal cancer; however, she had no personal medical history and was receiving non-steroidal anti-inflammatory drugs for joint pain. The patient was a non-smoker and had no occupational history of exposure to noxious substances.

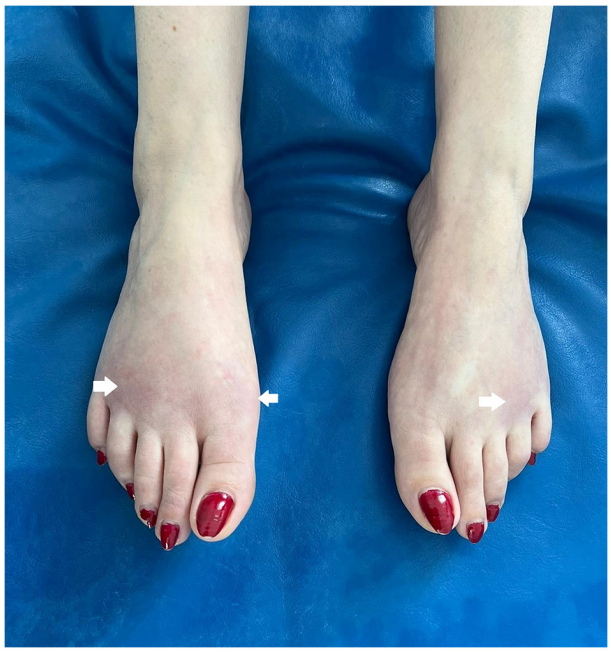

Figure 3. Discrete cyanotic skin areas on the dorsal face of both feet (white arrows).

On physical examination, the patient was clinically stable and had microstomia and perioral radial furrows (Fig. 1A and B), slight skin induration of the hands (Fig. 2) and discrete cyanotic skin areas on the dorsal face of both feet (Fig. 3). The patient also had asymmetric bilateral crepitant rales, bun normal vital signs (normal temperature, oxygen saturation on pulse-oximetry of 98%, blood pressure of 110/80 mmHg, heart rate of 100 beats/min and regular cardiac rhythm).

Laboratory findings at admission revealed normal blood count with non-specific biological inflammatory syndrome, consisting of high erythrocyte sedimentation rate (74 mm/h; normal, <20 mm/h) and high C-reactive protein (111.15 mg/l; normal, <5 mg/l), mild cytolysis with high alanine aminotransferase (82 U/l; normal, <55 U/l), high aspartate aminotransferase (53 U/l; normal, <34 U/l) and high gamma-glutamyl transferase (158 U/l; normal, <34 U/l). Urine analysis revealed no microscopic hematuria or proteinuria.

The patient was initially suspected of systemic sclerosis due to the appearance of microstomia and slight skin induration of the hands with diffuse arthralgia and myalgia, but with negative anti-SCL70 and anti-centromere B antibodies (Table I). Also, nailfold capillaroscopy showed a normal aspect of the capillary bed. Cryoglobulins were absent and the patient was seronegative for hepatitis B surface antigen and antibodies to hepatitis C. Antiphospholipid syndrome tests (anticardiolipin screening and anti-β2-glicoprotein I screening) were negative, but high titers (>100 U/ml) of MPO-ANCA were detected (Table I). Since the patient did not exhibit vasculitis, the diagnosis required further investigation to exclude other connective tissue diseases. In this sense, rheumatoid factor, antinuclear antibodies [indirect immunofluorescence (IIF); titer of 1:320 with homogeneous nuclear appearance] and

Table I. Patient's serology (routine laboratory diagnostic tests).

| Test/antibody[a] | Value | Normal range |
|---|---|---|
| Rheumatoid factor | 60.1 U/l | 0.0-30.0 U/l |
| Anti-citrullinated protein antibody | 10.8 U/l | <20.0 U/l |
| Systemic sclerosis panel (serum, Line Blot) | | |
| Anti-SCL70 | Negative | Negative |
| Anti-centromere A | Negative | Negative |
| anti-centromere B | Negative | Negative |
| Anti-RNA polymerase III 11 kDa | Negative | Negative |
| Anti-RNA polymerase III 155 kDa | Negative | Negative |
| Anti-fibrillarin | Negative | Negative |
| Anti-NOR90 | Negative | Negative |
| Anti Th/To | Negative | Negative |
| Anti-PM-SCL100 | Negative | Negative |
| Anti-PM-SCL75 | Negative | Negative |
| Anti-Ku | Negative | Negative |
| Anti-PDGFR | Negative | Negative |
| Anti-Ro52 | Negative | Negative |
| ANCA[b] | 1:80 | Negative |
| MPO-ANCA | 100 U/ml | <5 U/ml |
| PR3-ANCA | 2.4 U/ml | <5 U/ml |
| Antinuclear antibodies[b] | 1:320 | <1:160 |
| Anti-BPI | 1.9 U/ml | <10.0 U/ml |
| Anti-cathepsin G | 3.2 U/ml | <10.0 U/ml |
| Anti-lactoferin | 0.9 U/ml | <10.0 U/ml |
| Anti-lyzozyme | 1.3 U/ml | <10.0 U/ml |
| Anti-Sm | 1.3 U/ml | <15.0 U/ml |
| Anti-U1RNP | 2.4 U/ml | <25.0 U/ml |
| Anti-SSA (anti-Ro) | 4.8 U/ml | <15.0 U/ml |
| Anti-SSB (anti-La) | 2.2 U/ml | <15.0 U/ml |
| C3 serum complement | 1.8 g/l | <1.8.0 g/l |
| C4 serum complement | 0.3 g/l | <0.4.0 g/l |
| Anti-cardiolipin screening | 5.5 U/ml | <10.0 U/ml |
| Anti-β2-glicoprotein I screening | 2.3 U/ml | <10.0 U/ml |
| Anti-C1q IgG | 1.8 U/ml | <10.0 U/ml |
| Cryoglobulins | Negative | Negative |
| Anti-Jo 1 | 1.6 U/ml | <15.0 U/ml |
| Hepatitis B surface antigen | Negative | Negative |
| Anti-hepatitis C virus | Negative | Negative |

[a]Antibodies are measured in U/l or U/ml and complement in g/l; [b]tested by indirect immunofluorescence. PDGFR, platelet-derived growth factor receptor; ANCA, antineutrophil cytoplasmic autoantibodies; MPO, myeloperoxidase; PR3, proteinase 3; U1RNP, U1 small nuclear ribonucleoprotein; anti-SS, anti-Sjögren's-syndrome-related antigen.

anti-double-stranded DNA antibodies were positive (Table I). During hospitalization, the patient experienced an episode of swelling, forefoot erythema and local heat (predominantly in the fourth and fifth right fingers), associated with severe local pain. Simultaneously, the patient developed febrile episode (38.6˚C). The patient's rapid COVID-19 antigen test was negative. Musculoskeletal ultrasound examination of the forefoot revealed subcutaneous edema, negative power Doppler signal and no synovitis or tenosynovitis.

High resolution computerized tomography (CT) scan revealed interlobular septal thickening, reticulations, tubular bronchiectasis with thickened walls, some of which were with free lumen and others occupied by mucus (Fig. 4A), accompanied by small areas of pulmonary consolidation and ground glass alveolar opacities, which were located predominantly in both lower lobes (posterior segments) with peripheral topography (Fig. 4B and C). This imaging aspect raised the suspicion of early-stage interstitial lung disease (ILD). Moreover, isolated

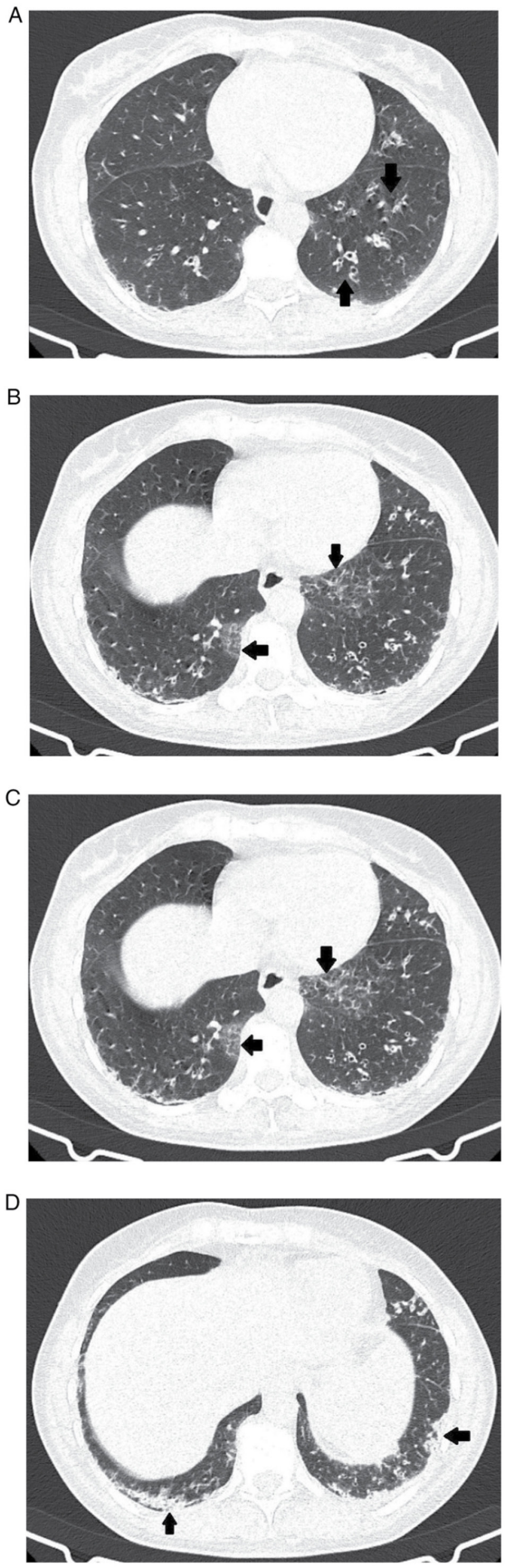


Figure 4. (A) Interlobular septal thickening, reticulations, tubular bronchiectasis with thickened walls, some with free lumen and others occupied by mucus (black arrows). (B) Small areas of pulmonary consolidation and (C) ground glass alveolar opacities located predominantly in both lower lobes with peripheral topography (black arrows). (D) Isolated subpleural interstitial lung micronodules (black arrows).

subpleural interstitial lung micronodules were detected. The biggest micronodules measured 4 mm (in the anterior segment of the right upper lobe) and 5 mm (in the lateral segment of the middle lobe, subpleural in the lower segment of the lingula), probably with an inflammatory substrate (Fig. 4D). The esophagus was presented as having increased caliber in the whole trajectory (distended by air) (data not shown).

Therefore, the diagnosis of MPA was formulated considering the symptoms, the clinical findings and the high tither of anti-MPO antibodies. Other vasculitides were excluded [the patient had negative cytoplasmic (c)-ANCA, no pulmonary hemorrhage and normal serum eosinophile count], as well as systemic lupus erythematosus (SLE; normal serum complement level, absence of proteinuria, normal blood count and absence of skin involvement) and systemic sclerosis (negative anti-SCL70 and anti-centromere B antibodies, normal nailfold capillaroscopy and absence of proteinuria).

For the febrile episode, the patient was treated with intravenous acetaminophen (1 g/day), intramuscular dexamethasone (4 mg/day) and oral colchicine (1 mg/day) for 7 days, with complete resolution of signs and symptoms.

After this initial treatment, when infection became unlikely and immunology results indicated an autoimmune etiology, the patient received intravenous dexamethasone (8 mg/day) and oral treatment with pantoprazole (20 mg/day), potassium aspartate (39 mg/day) and magnesium aspartate tetrahydrate (12 mg/day) for 10 days. After the diagnosis of MPA was formulated, the patient received a 3-day course of intravenous pulse-therapy with methylprednisolone (500 mg/day), followed by oral methylprednisolone (40 mg/day) and subcutaneous methotrexate (10 mg). After following this treatment, at discharge, the patient's general condition improved with the remission of myalgia and arthralgia.

At discharge, the patient was prescribed treatment with subcutaneous methotrexate (15 mg/week, increased after 1 week to 20 mg/week), combined with oral methylprednisolone (40 mg/day, with progressive dose reduction and received together with pantoprazole 20 mg/day) and oral diet supplements (folic acid 5 mg/day, potassium aspartate 39 mg/day, magnesium aspartate tetrahydrate 12 mg/day and vitamin D 2000 IU/day).

After 5 months of treatment with progressive decreasing methylprednisolone doses namely a decrease of 0.1-0.2 mg/kg every 2 weeks (for example, after taking 32 mg/day for 2 weeks, the dose was reduced to 24 mg/day for the following 2 weeks) combined with methotrexate 20 mg/week, the patient's general condition improved with absence of febrile state, arthralgia or myalgia and remission of subcutaneous edema. Laboratory findings after 5 months of follow-up showed the absence of biological inflammatory syndrome and absence of anti-SCL70 and anti-centromere antibodies. In addition, no renal damage was apparent, the patient having normal serum creatinine levels and absence of proteinuria or hematuria.

The absence of systemic sclerosis-specific antibodies, both at the first evaluation and the subsequent re-evaluations, and the normal aspect of the capillary bed at nailfold capillaroscopy along with favorable clinical and biological response to cortisone treatment, rendered the diagnosis of systemic sclerosis unlikely.

Table II. American College of Rheumatology/European Alliance Associations for Rheumatology 2022 classification criteria for microscopic polyangiitis[a].

| Criteria | Score | Present patient |
|---|---|---|
| ANCA/MPO-ANCA positivity | +6 | +6 |
| Pauci-immune glomerulonephritis | +3 | 0 |
| Lung fibrosis/ILD | +3 | +3 |
| Sino-nasal symptoms/signs | -3 | 0 |
| Cytoplasmic ANCA/PR3-ANCA positivity | -1 | 0 |
| Eosinophil count $\geq 10^9$/l | -4 | 0 |
| Total score | ≥+5 | +9 |

[a]After excluding vasculitis mimics, a patient with small/medium vessel vasculitis could be classified as having microscopic polyangiitis with a cumulative score of ≥5 points with 91% sensitivity and 94% specificity (23). ANCA, antineutrophil cytoplasmic autoantibodies; MPO, myeloperoxidase; PR3, proteinase 3; ILD, interstitial lung disease.

## Discussion

MPA is a rare disease that was initially considered to be a microscopic form of polyarteritis nodosa (PAN) due to similar clinical manifestations (6). In 1985, with the discovery of ANCA antibodies, which are present in three types of vasculitis that involve small vessels (MPA, GPA and EGPA) and are absent in PAN, a differentiation between the two was possible (6). Thus, in 1994 at the International Chapel Hill Consensus Conference (CHCC), MPA was defined as a separate entity associated with MPO-ANCA, with absent immune complex deposition and with the presence of pulmonary capillaritis and glomerulonephritis (6-7). Subsequently, in 2012, the CHCC revised the nomenclature of systemic vasculitis, and MPA was defined as a form of necrotizing vasculitis, with minimal or without immune deposits, which predominantly involves small vessels (capillaries, venules and arterioles), but may also involve medium vessels with absent granulomatous inflammation (1).

IIF can identify two major types of ANCAs: C-ANCA and the perinuclear (p)-ANCA. Using enzyme-linked immunosorbent assay (ELISA), c-ANCA was shown to be specific for PR3 (PR3-ANCA) and p-ANCA to be specific for MPO (MPO-ANCA) (8). ANCAs are biomarkers used in the diagnosis of small-vessel vasculitis (MPA, GPA and EGPA) that should be detected using IIF, according to the 1999 international consensus on ANCA testing (9). In addition, in case of a positive result with IIF, a distinction using ELISA should be made between the two types of ANCA, anti-MPO-ANCA and anti-PR3-ANCA, due to the important clinical and pathogenic implications (9).

The revised 2017 international consensus proposed by a group of international experts (from the United States of America, Europe, Asia and Australia) emphasizes the importance of ANCA in diagnosis, but not as a follow-up tool for patients with AAV (10). The same international consensus recommends high-quality immunoassays for PR3-ANCAs and MPO-ANCAs as the preferred method for diagnosing AAV. Moreover, it does not consider IIF necessary. The recommendation applies to AAV (particularly GPA and MPA) but does not apply to the diagnosis of inflammatory bowel disease (IBD), immune hepatitis and drug-induced autoimmunity (10).

Patients with AAV are usually seropositive for PR3-ANCA or MPO-ANCA, but do not have both positive autoantibodies. In MPA, it was found that 90% of patients are seropositive for ANCA at diagnosis, ~55% being anti-MPO-ANCA positive. In GPA, at the time of diagnosis, ANCA are present in 95% of patients, who are mostly anti-PR3-ANCA positive (~65%). In EGPA, 40% of patients are positive for ANCA, usually anti-MPO-ANCA (11,12). ANCAs can also be found in other chronic inflammatory conditions, such as IBD (seropositivity for p-ANCA in 50-67% of patients with ulcerative colitis and 6-15% of those with Crohn's disease) and liver disease [primary sclerosing cholangitis (88%), primary biliary cirrhosis, autoimmune hepatitis (81%) and chronic viral hepatitis]. In these diseases, p-ANCA is atypical and not anti-MPO (13-17). Certain studies confirm the simultaneous existence of AAV and IBD, but the association is rare. In a previously reported case, IBD occurred for a few years before the onset of AAV (18). ANCAs may also be positive in rheumatoid arthritis, SLE, malignant hematological diseases (19), as well as in infectious endocarditis and tuberculosis (20-22). In the current patient, the presence of p-ANCA was detected using ELISA and IIF, followed by confirming the intense positivity of MPO-ANCA through ELISA.

In 2022, an international group of researchers formulated and validated several criteria for classifying and differentiating the three types of AAV (23). These criteria have been approved by the American College of Rheumatology and the European Alliance Associations for Rheumatology. The study included 149 patients with MPA and 408 healthy comparators. Out of 10 items identified by regression analysis, the authors retained the following six criteria: i) P-ANCA/MPO-ANCA positivity (+6); ii) pauci-immune glomerulonephritis (+3); iii) PF or ILD (+3); iv) sino-nasal symptoms or signs (-3); v) c-ANCA or PR3-ANCA positivity (-1); and vi) eosinophil count $\geq 10^9$/l (-4) (Table II). These criteria have a sensitivity of 91% and a specificity of 94%. At a cumulative score of ≥5 the patient is classified as having MPA. An important point to note is that these criteria should be used after the diagnosis of vasculitis of small or medium vessels and after other conditions that mimic vasculitis have been excluded (23). Applying these criteria, the present patient accumulated a total of nine points due to anti-MPO-ANCA positivity, the presence of ILD

and the absence of sino-nasal symptoms or signs, renal damage and anti-PR3 antibodies, as well as normal eosinophil count. An important observation of these criteria reveals an equal score between renal and pulmonary involvement. Thus, MPA can be classified as vasculitis of small/medium vessels with PF or ILD and without renal impairment if there is positivity for anti-MPO-ANCA, normal eosinophil count and the patient has no sino-nasal symptoms or signs (Table II).

It is known that rapidly progressive glomerulonephritis is a common manifestation of MPA. Renal involvement has been indicated to occur in almost all cases in the first series of reported cases of MPA, but according to the third edition of the European Alliance Associations for Rheumatology Textbook on Rheumatic diseases, this can be attributed to the fact that the first cases were reported by nephrologists (24).

The results of a 2018 study on 97 patients diagnosed with MPA meeting the CHCC 2012 criteria, which were followed up for a median period of 47.6 months, showed the following: The median age at the onset of symptoms was 50.7 years, 66% of patients were positive for MPO-ANCA, 24.7% for PR3-ANCA and the remaining 9.3% were undifferentiated ANCA. A total of 79.4% of patients had pulmonary involvement, this being present in 55.8% of patients at the time of diagnosis, the remaining 44.2% developing symptoms and signs during follow-up. The most common identified CT patterns were pulmonary infiltrates (50.5%) and ground glass opacities (40.2%). Diffuse alveolar hemorrhage had been present since the onset of the disease in 15.5% of patients, and it was developed by 30% of all patients. PF was the most common involvement at the end of follow-up, being present in 53.6% of patients. It was noted that, at the end of follow-up, interstitial changes from the onset of the disease were associated with the development of PF and bronchiectasis. This study concluded that in patients with MPA the signs of ILD were usually reversible, and predicted a higher incidence of PF changes and bronchiectasis at the end of follow-up (25).

A study conducted by a group of researchers from Greece, published in 2010, included a group of 33 patients diagnosed with MPA who were followed up for a mean of 38 months. The authors reported that the most common manifestations were nonspecific symptoms, such as fever, fatigue and weight loss. This study demonstrated and emphasized that PF is a common manifestation (39%) and a leading cause of death in patients with MPA. They also concluded that PF may be manifested at the time of diagnosis (36%) or may occur before other manifestations (3%) of MPA (26). Similarly, in the present case report, the patient presented weight loss and episodes of fever. The diagnosis of PF in the early stages was concomitant with the diagnosis of MPA.

In a retrospective study performed in China, out of 67 MPA cases, 19 patients (28%) presented with PF with a median age of 63.6 years (27). All patients had non-specific biological inflammatory syndrome and were positive for MPO-ANCA. The following were the most common manifestations: Fever (89.5%), cough (84.2%), dyspnea (78.9%) and velcro rales (84.2%). This study found that 36.8% of cases presented fever before the diagnosis of PF and 63.2% after the diagnosis. In addition, the remission of febrile episodes after the administration of glucocorticoids was noticed in most cases, with no benefit from antibiotic therapy. The patient of the present case report presented two of the symptoms identified as the most common in the aforementioned study, such as fever and velcro rales. Regarding the febrile episode in the present case report, the patient recovered after glucocorticoids without the use of antibiotic therapy. In addition, apart from fever, the patient showed no other clinical or biological signs of infection.

A retrospective review from Argentina of 28 patients with MPA who were divided into two subgroups, with PF (MPA-PF) and without PF (MPA-non-PF), revealed that 9 patients (32%) were classified as MPA-PF. This subgroup had more respiratory symptoms and higher mortality than the MPA-non-PF subgroup. In 5 patients (17%) PF preceded other manifestations of vasculitis (28).

In a study on a cohort of 85 patients (47 men and 38 women) who met the CHCC 2012 criteria for MPA, it was found that in addition to renal manifestations (78.8%), weight loss (72.9%), skin changes (62.4%) and fever (55.3%), more than half of the patients had joint pain (50.6%). Myalgias were present in 48.2% of patients (29).

Following analysis of these studies, it can be concluded that general symptoms, such as fever, fatigue or weight loss, are common manifestations of MPA. The prevalence of ILD in patients with MPA is quite prevalent worldwide, being common at the time of diagnosis of MPA. Most patients are seropositive for MPO-ANCA, but they may also be PR3-ANCA positive or have an undifferentiated-ANCA disease.

In the present case report, although the initial clinical presentation was not suggestive of a vasculitis-type pathology, this diagnosis was later highlighted during hospitalization by the cyanotic skin changes, the subcutaneous edema associated with the febrile episode and the paraclinical investigations. Unfortunately, lung biopsy was not performed considering that the early diffuse interstitial lung lesions were minimal and difficult to approach. In addition, the patient required urgent treatment because of deteriorating condition. Obtaining the result of a lung biopsy would have taken too long, jeopardizing the clinical evolution. Thus, the main guiding significance of the present case is that even in the absence of renal damage the diagnosis of MPA should not be excluded by the clinician.

In conclusion, MPA is a necrotizing systemic vasculitis that affects small and medium-sized vessels and has long been thought to affect the kidneys most frequently. The current case report presented a patient with MPA, with constitutional and musculoskeletal symptoms, atypical skin changes, intense positivity for MPO-ANCA, in whom renal dysfunction was absent, while ILD was present.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

DIM, AM and AR participated in the design of the case report and wrote the manuscript. DIM, ALC and CP were responsible for the patient evaluation and management. VG, MD and DGM were responsible for analysis and interpretation of data and critically reviewed the manuscript. All authors confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Written informed consent was obtained from the patient prior to publication at the time of admission.

## Competing interests

The authors declare that they have no competing interests.

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