Abstract

**Aim:** We are reporting a case of an unusual presentation of granulomatosis with polyangiitis (GPA) with liver involvement. **Case presentation:** A 45-year-old male patient presented with erythematous plaques on the face and bilateral nasal obstruction. On physical examination, the patient had a ring-shaped squamous plaque on the face. The laboratory findings revealed an accelerated erythrocyte sedimentation rate at 100 mm/h, an elevated C-reactive protein at 66 mg/L, hyper gamma globulinemia 16 g/L, and an elevated alkaline phosphatase (twice the upper normal limit). The craniofacial and thoracoabdominal computed tomography (CT) scans showed ethmoid and maxillary sinusitis, low facial bone density, multiple mediastinal and hilar lymphadenopathy, diffuse small pulmonary nodules, and hepatomegaly. A cutaneous lesion biopsy, the nasal mucosa, and the liver showed a chronic inflammatory granulomatosis process with necrosis. Serum anti-neutrophil cytoplasmic antibody (ANCA) against PR3 was positive. The clinical, biological, radiological, and histological findings substantiated the diagnosis of GPA. The patient received systemic steroids combined with cyclophosphamide pulses on days 1, 14 and 28 and then he was
lost to follow-up. Two-years later, he presented with a cardiac failure and skin ulcer in the right lower limb. A nasal endoscopic exam showed nasal septum cartilage perforation with resorption of the middle and inferior nasal concha. Two weeks later, he developed a diffuse alveolar hemorrhage and was therefore transferred to the intensive care unit but died of respiratory failure 3 days later. 

**Conclusion:** Clinicians should be aware of GPA atypical clinical manifestations.

**Keywords**
Granulomatosis with polyangiitis, Skin lesions, Necrotizing granulomatosis hepatitis, Case report.
Introduction
Granulomatosis with polyangiitis (GPA) is an anti-neutrophilic cytoplasmic antibody (ANCA) associated systemic small vessel vasculitis with a necrotizing granulomatous inflammation. It was described for the first time by Friedrich Wegener in 1936. GPA has a wide spectrum of clinical manifestations making it a challenging diagnostic dilemma for clinicians. The diagnosis is based on the association of clinical features, laboratory tests, and histological findings. The condition is mainly characterized by necrotizing granulomatosis of the upper and lower respiratory tract and by glomerulonephritis. However, the granulomatosis inflammation or the vasculitis can affect any organ. Liver involvement in patients with GPA was rarely reported. We are reporting a case of an unusual presentation of GPA involving the upper airways, lungs, skin, and the liver with lethal cardiac manifestations.

Patient and observation
Patient
A 45-year-old Tunisian male patient working as a professor, who had no relevant family history presented with erythematous plaques on the face and bilateral nasal obstruction. He reported fatigue, loss of appetite, and unintentional weight loss with mouth and eye dryness for several months.

Figure 1. A ring-shaped squamous plaque on the face.
Clinical findings
On physical examination, the patient had a ring-shaped squamous plaque on the face (Figure 1) and unilateral submandibular lymphadenopathy. A nasal endoscopy found congested nasal mucosa with bloody crusts while laryngoscopy showed increased thickness of the right vocal cord and paralysis of the left vocal cord. The ophthalmological examination concluded a low tear break-up time. The pulmonary auscultation revealed bibasilar crepitations and abdominal palpation hepatomegaly. A biopsy was performed in the cutaneous lesion showing a granulomatosis inflammation.

Diagnosis assessment
The laboratory findings showed an accelerated erythrocyte sedimentation rate (100 mm/h), an elevated C-reactive protein (66 mg/L), hyper gamma globulinemia (16 g/L), and an elevated alkaline phosphatase (twice the upper normal limit). The rest of the lab tests including cell blood count, creatinine, electrolytes, angiotensin-converting enzyme, aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltransferase, GGT were normal. Urinalysis was negative for glucosuria, proteinuria, and blood cells. Serological tests for bacterial and viral infections including hepatitis B, hepatitis C were also negative. QuantiFERON-TB Gold In-Tube (QFT-G) test for the diagnosis of tuberculosis disease was negative suggesting that there is not TB infection.

A nasal mucosa biopsy revealed a granulomatosis inflammation with necrosis.

The craniofacial and the thoracoabdominal computed tomography (CT) scans showed ethmoid and maxillary sinusitis, low facial bone density (Figure 2), multiple mediastinal and hilar lymphadenopathy, diffuse small pulmonary nodules, peripheral, linear reticulations with subpleural cystic lesions, compatible with fibrosis, and hepatomegaly. Plethysmography showed a restrictive pattern with normal forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio and severely diminished Total Lung Capacity (TLC of 64 per cent of the predicted level) and Forced Vital Capacity (FVC of 60 per cent of the predicted level). Autoimmune serology, including assays for auto-antibodies against nuclear antigen, SS-A/SS-B, anti-cyclic citrullinated peptide (anti-CCP), anti-ds-DNA was negative. Our patient had c-ANCA positivity with a titer of 1:40 (< 1:20). P-ANCA was negative. Proteinase 3 antibody (anti-PR3) was positive by an immunodot technique (Euroimmun, Germany). The serology was negative for autoimmune hepatitis and primary biliary cholangitis.

The clinical, biological, radiological, and histological findings substantiated the diagnosis of GPA.

Since liver involvement was suspected, a liver biopsy was also performed and was positive on H&E staining for chronic inflammatory granulomatosis process without necrosis.

Figure 2. Ethmoid and maxillary sinusitis and low facial bone density.
Therapeutic intervention
The patient received systemic steroids initiated by a 3-day regimen of methylprednisolone at a dose of 1 g a day, then oral prednisone at a dose of 1 mg/kg/day combined with cyclophosphamide pulses at a dose of 0.6 mg/m² on days 1, 14 and 28. Then he was lost to follow-up.

Follow-up and outcome
Two years later, he was readmitted for dyspnea on exertion, oedema of the lower limbs, and a painful ulcer of his leg that had appeared 3 months prior to admission. On examination, he had tachypnea with a respiratory rate of 34 breaths/min, a large ulcer with necrosis and pus in the right leg (Figure 3), and severe peripheral pitting oedema. The nasal endoscopic exam showed nasal septum cartilage perforation with resorption of the middle and inferior nasal concha. The lab tests revealed a biological inflammatory syndrome and elevated alkaline phosphatases. Pus culture was positive for *Pseudomonas aeruginosa*. A skin biopsy showed leukocytoclastic vasculitis. An electrocardiogram revealed a bifascicular block and a transthoracic echocardiography showed a dilated right ventricle, a pericardial effusion, a tricuspid valve regurgitation, and a pulmonary artery pressure of 80 mmHg. The patient received antibiotics to treat his skin infection and intravenous diuretics and oxygen via nasal cannula to manage his heart congestive failure. He was also started on three methylprednisolone pulses relayed by oral corticosteroids and cyclophosphamide. Two weeks later, he developed a diffuse alveolar hemorrhage. He was transferred to the intensive care unit, but died of respiratory failure 3 days later.

Discussion
GPA is a severe life-threatening multi-systemic vasculitis usually involving the upper and lower respiratory tract and the kidneys. However, it may involve other organs with variable clinical presentations.

Our patient initially presented with upper airways signs, pulmonary symptoms, skin lesions and liver involvement. The diagnosis of GPA was based on the combination of clinical manifestations with serological and histological evidence.

The liver involvement was confirmed by cholestasis and a chronic inflammatory granulomatosis process in the biopsy, which made this case worth reporting. In fact, although granuloma and/or the vasculitis may be found in any organ, the liver does not belong to the major target organs compared to the upper and lower airways. In fact, nasal and sinus involvement is the most common GPA manifestation. Up to 85% of patients present with necrotizing granulomatosis lesions in the nasal cavity and sinuses. The most frequent clinical features are nose crusting, blood stained rhinorrhea and nasal obstruction. Pulmonary involvement is slightly less common and occurs in about 80% of patients with a wide

**Figure 3. A large ulcer with necrosis and pus in the right leg.**
spectrum of lesions. Nodules are the most common radiological features. Cavitation is a hallmark of the disease but it is only found in 22% of patients. Liver involvement in patients with GPA is not quite clear. It has been demonstrated that the liver is frequently affected in patients with active GPA when the affection is mirrored by liver test abnormalities. The biochemical picture during active disease revealed both a cholestatic pattern (i.e. increased g-GT and ALP) as well as a hepatocellular pattern (with increased ALT and AST) and was found in 2% to 25% patients with GPA at the time of diagnosis and was associated with a severe disease course and a poor prognosis. However, necrotizing granulomatosis hepatitis in liver biopsy was rarely reported. To the best of our knowledge, this might be the fifth case of hepatic involvement granulomatosis hepatitis reported in the literature. All that cases were revealed by a persistent elevation of liver biological parameters and confirmed by liver biopsies after excluding adverse drug affects, viral hepatitis, alcoholic or ischaemic hepatitis. The serology was also negative for autoimmune hepatitis and primary biliary cholangitis, and the liver biopsies did not show evidence for these diseases. All patients in the literature unlike the patient in this case, responded to aggressive immunosuppressive drugs.

Furthermore, it would be interesting to note that the patient presented with a squamous erythematous plaque in the face as the initial presentation of the disease, which is particularly unusual since typical skin lesions in GPA consist of palpable purpura, papules, subcutaneous nodules and more rarely pyoderma-gangrenosum such as ulcers, digital ulcerations and gangrenes. In fact, the cutaneous involvement in GPA is common and can be the revealing presentation in more than 30% of cases. The spectrum of skin lesions is very large. They can be classified as specific or nonspecific depending on the presence of histopathological evidence of vasculitis with or without granuloma. Despite the unusual clinical presentation, the histological findings consisted of specific skin lesions in an ANCA associated vasculitis.

Mortality rate associated with GPA is as high as 80% in untreated patients. The conventional treatment for severe GPA consists of combination of high doses of systemic glucocorticoid and immunosuppressant agents which have contributed to the improvement of the prognosis of patients with GPA. However, these patients are still at risk of various complications. Several clinical factors were identified to predict higher mortality rates. In fact, liver involvement was proven to be related to the disease activity and to predict poor clinical outcomes.

In this case, the patient had pulmonary fibrosis PF complicated with pulmonary hypertension. PF is an uncommon manifestation observed in patients with ANCA vasculitis. It is associated with worse prognosis.

In the present case, the patient did not comply with the treatment. He presented after two years with acute heart failure with a rapidly progressive fatal outcome. He had an acute congestive heart with concomitant pericarditis, dilated cardiomyopathy, valvular dysfunction and conduction defect which is extremely exceptional in this pathology. Although cardiac involvement is considered to be uncommon in patients with GPA, the condition could be life threatening. This manifestation is probably underestimated since it lacks specificity. In fact, depending on the series and the methods applied such as electrocardiogram, echocardiography or cardiac magnetic resonance imaging (MRI), the prevalence of cardiac manifestations ranged between 40% and 60% of the patients. Pericarditis is the most common cardiac manifestation and was reported in up to 35% of patients, followed by cardiomyopathy [30%] and coronary artery disease (12% of the patients). Valve disease and conduction disorder including intraventricular conduction defects and atrioventricular blockage are less common. As a result of aggressive treatment, cardiac involvement in patients with GPA was not associated with poorer outcome. In this case the patient died from a respiratory failure due to diffuse alveolar hemorrhage which can be, either another rare and mortal complication of GPA occurring in only 5% to 10% of the patients, or a complication of the acute heart failure. In another hand, necrotizing granulomatosis hepatitis could increase the risk of heart failure. The pathogenesis of death in this case might be multifactorial.

Conclusion
The goal of presentation of this case was to present some rare and unusual manifestations of granulomatosis with polyangiitis presenting with hepatic granuloma and pulmonary fibrosis pulmonary fibrosis. Clinicians should be aware of liver involvement because it can be life-threatening. Systemic corticosteroids and immunosuppressant drugs remain the mainstay in the treatment of this potentially fatal disease. However, the frequencies of these atypical manifestations are to be studied in patients with GPA.

Declarations
Ethics approval
Not applicable.
Consent for publication
Written informed consent was obtained from the patient’s next of kin for publication of this case report and any accompanying images.

Authors’ contributions
Ichrak Bannour, Marwa Ben Brahim, Olfa Berriche, Sondes Arfa, Asma Ben Mabrouk and Sonia Hammemi all contributed equally to the conception, design, drafting and revising of the manuscript. All authors read and approved the final manuscript.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Acknowledgement
The authors thank the entire staff of the Department of Internal Medicine at Mahdia University Hospital (Tunisia) for their contribution in the management of the patient.

References
Open Peer Review

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Version 3

Reviewer Report 20 July 2023

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I approved the new version.

Only have one suggestion, please edit this typewriting mistake:

"The goal of presentation of this case was to present some rare and unusual manifestations of granulomatosis with polyangiitis presenting with hepatic granuloma and pulmonary fibrosis pulmonary fibrosis".

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Rheumatologist and immunology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 20 Jul 2023

Ichrak Bannour

I do want to thank the reviewer Professor Gloria Vasquez for her corrections and suggestions of improvement. I corrected the typewriting mistake and omitted the expression "pulmonary fibrosis"

Competing Interests: No competing interests were disclosed.
I have reviewed the corrected version of the article, I realize that most of the suggestions were followed, but I still have doubts about the case and comments.

1. The cause of pulmonary hypertension described as “Showed a dilated right ventricle, a pericardial effusion, a tricuspid valve regurgitation, and a pulmonary artery pressure of 80mmHg” is not clear.

2. They describe an Immunodot technique to measure antiproteinase 3 levels, could you give the name of the brand?

3. In the discussion it is added that the heart failure of the patient is due to compromise by the disease, but the heart failure is right according to the echocardiography and associated with pulmonary hypertension, which is very rare.

4. Figure 3 is titled as a granulomatous lesion, but the granulomas are not shown or seen.

5. This sentence in the final conclusion is contradictory and I think that statement cannot be made "This case demonstrates that atypical clinical manifestations of GPA are very frequent".

6. I think it should be made clear that quantiferon, although it is positive in the presence of active tuberculosis, can also be positive in latent tuberculosis and is not a good diagnostic tool for active tuberculosis.

For all these reasons I still do not think the case is ready to be indexed.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Rheumatologist and immunology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
Reviewers comments

1. The cause of pulmonary hypertension described as “Showed a dilated right ventricle, a pericardial effusion, a tricuspid valve regurgitation, and a pulmonary artery pressure of 80mmHg” is not clear.

We thank the reviewer for underscoring this point which allows us to add that the patient had pulmonary fibrosis which could explain the pulmonary hypertension.

In fact, we added in line 41-47: that CT scan showed “peripheral, linear reticulations with subpleural cystic lesions, compatible with fibrosis. Plethysmography showed a restrictive pattern with normal forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio and severely diminished Total Lung Capacity (TLC of 64 per cent of the predicted level) and Forced Vital Capacity (FVC of 60 per cent of the predicted level).” The causes of the pulmonary fibroses were screened “Autoimmune serology, including assays for auto-antibodies against nuclear antigen, SS-A/SS-B, anti-cyclic citrullinated peptide (anti-CCP), anti-ds-DNA, Rnase protection (RNP), sphingomyelin (SM), anti-Saccharomyces cerevisiae antibodies (ASCA IgA and ASCA IgG), was negative.” And our patient had “c-ANCA positivity with a titer of 1:40 (<1:20). P-ANCA was negative. Proteinase 3 antibody (anti-PR3) was positive by an immunodot technique. The serology was negative for autoimmune hepatitis and primary biliary cholangitis.”

2. They describe an Immunodot technique to measure antiproteinase 3 levels, could you give the name of the brand?

We are grateful to the reviewer for this comment. And we added in line 49 that the Immunodot technique to measure antiproteinase 3 levels was from (Euroimmun, Germany).

3. In the discussion it is added that the heart failure of the patient is due to compromise by the disease, but the heart failure is right according to the echocardiography and associated with pulmonary hypertension, which is very rare.

We are grateful to the reviewer for this comment. The patient had lung fibrosis (probably due to his vasculitis) leading to a restrictive lung syndrome with pulmonary hypertension and right ventricular dysfunction. And he had also pericarditis which is the most common cardiac manifestation and was reported in up to 35% of patients.

4. Figure 3 is titled as a granulomatous lesion, but the granulomas are not shown or seen.

We thank the reviewer for this comment. Unfortunately, we had not found a clear figure illustrating granuloma in the hepatic lesions. And as the case is very old I haven’t found the slides for proofreading. So I deleted the figure.

5. This sentence in the final conclusion is contradictory and I think that statement cannot be made “This case demonstrates that atypical clinical manifestations of GPA are very frequent”.

We thank the reviewer for underscoring this point which allows us to add that “The goal of presentation of this case was to present some rare and unusual manifestations of granulomatosis with polyangiitis presenting with hepatic granuloma and pulmonary fibrosis”.

Ichrak Bannour
5. I think it should be made clear that quantiferon, although it is positive in the presence of active tuberculosis, can also be positive in latent tuberculosis and is not a good diagnostic tool for active tuberculosis. We thank the reviewer for underscoring this point. The QuantiFERON(R) TB Gold (in Tube) assay is intended for use as an aid in diagnosis of TB infection. Negative results suggest that there is not TB infection. A positive test indicates that a person has been infected with TB bacteria. It does not tell whether the person has latent TB infection or has progressed to TB disease.

**Competing Interests:** No competing interests were disclosed.

Author Response 30 Jun 2023

Ichrak Bannour

In this version we precised that pulmonary fibrosis is the cause of the pulmonary hypertension and the heart failure "a dilated right ventricle, a pericardial effusion, a tricuspid valve regurgitation, and a pulmonary artery pressure of 80mmHg". Second, we described the Immunodot technique used to measure antiproteinase 3 levels. Third, we deleted the figure 3 because we had not found a clear figure illustrating granuloma in the hepatic lesions. Than, we changed the conclusion and cited the aims of this case. Finally, we cited that Quantiferon can also be positive in latent tuberculosis and is not a good diagnostic tool for active tuberculosis.

**Competing Interests:** No competing interests were disclosed.
In the initial evaluation of liver function, neither the levels of g-GT nor LA appear, in the presence of a granulomatous infiltration of the liver, these data are critical.

In the image of the liver biopsy, it would be worth pointing out the findings and specifying the site of the taking, the staining and the resolution of the image in the figure caption.

In the second part of the story, the patient arrives with right heart failure and pulmonary hypertension, its origin is not clear.

The discussion refers to seven cases of liver involvement in the literature but does not describe whether the findings were similar to the case described or different.

It is reported that liver involvement can be a cause of mortality but here the patient died of alveolar hemorrhage, so this aspect is not clear.

It would be useful to describe the title of the anti PR3.

The authors describe that tuberculosis was ruled out serologically, what type of test was used.

I think that all these details should be clarified, the discussion should be improved, in order to take advantage of a case that is very interesting.

**Is the background of the case's history and progression described in sufficient detail?**
Partly

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**
Partly

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**
Partly

**Is the case presented with sufficient detail to be useful for other practitioners?**
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Rheumatologist and immunology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
Ichrak Bannour

Reviewer comments

In the initial evaluation of liver function, neither the levels of g-GT nor LA appear, in the presence of a granulomatous infiltration of the liver, these data are critical.

We thank the reviewer for underscoring this point which allows us to add the initial evaluation of liver function in lines 31 and 33 “and an elevated alkaline phosphatase (twice the upper normal limit).” and “gamma-glutamyl transferase, GGT were normal”.

In the image of the liver biopsy, it would be worth pointing out the findings and specifying the site of the taking, the staining and the resolution of the image in the figure caption.

We are grateful to the reviewer for this comment. We pointed out in the liver biopsy Liver biopsy hepatic sinusoids with neutrophilic infiltration and microabscess formation. And we added in line 48, 49 and 50 “Liver biopsy showing hepatic sinusoids with neutrophilic infiltration and microabscess formation (arrows), H&E staining, 200× magnification.”

Figure 3. Chronic inflammatory granulomatosis process on biopsy: Liver biopsy showing hepatic sinusoids with neutrophilic infiltration and microabscess formation (arrows), H&E staining, 200× magnification.

In the second part of the story, the patient arrives with right heart failure and pulmonary hypertension, its origin is not clear.

We thank the reviewer for this remark. In this case the patient did not adhere to the immunosuppressive treatment and presented after two years with a rapidly lethal right heart failure. What made our patient different was the fact that he presented with an acute congestive heart with concomitant pericarditis, dilated cardiomyopathy, valvar dysfunction and conduction defect which is extremely exceptional. We precise in line 133-136 that “. He presented after two years with acute heart failure with a rapidly progressive fatal outcome. He had an acute congestive heart with concomitant pericarditis, dilated cardiomyopathy, valvular dysfunction and conduction defect which is extremely exceptional in this pathology”.

The discussion refers to four cases of liver involvement in the literature but does not describe whether the findings were similar to the case described or different.

As underlined by the reviewer, this was the fifth case of liver involvement described in the literature all revealed by a persistent elevation of liver biological parameters and confirmed by liver biopsies after excluding adverse drug affect, viral hepatitis, alcoholic or ischaemic hepatitis in all patients. The serology was also negative for autoimmune hepatitis and primary biliary cholangitis, and the liver biopsies did not show evidence for these diseases. All patients the literature unlike the patient in this case, responded to aggressive immunosuppressive drugs. This was added in line 109-114: “All that cases were revealed by a persistent elevation of liver biological parameters and confirmed by liver biopsies after
excluding adverse drug affects, viral hepatitis, alcoholic or ischaemic hepatitis. The serology was also negative for autoimmune hepatitis and primary biliary cholangitis, and the liver biopsies did not show evidence for these diseases. All patients in the literature unlike the patient in this case, responded to aggressive immunosuppressive drugs.”

It is reported that liver involvement can be a cause of mortality but here the patient died of alveolar hemorrhage, so this aspect is not clear.

We thank the reviewer for this remark which allowed us to clarify the cause of mortality of the patient in this case. “In fact, he died from a respiratory failure due to diffuse alveolar hemorrhage which can be, either another rare and mortal complication of GPA occurring in only 5% to 10% of the patients, or a complication of the acute heart failure. In another hand, Necrotizing granulomatosis hepatitis could increase the risk of heart failure”. The pathogenesis of death in this case might be multifactorial. We added this in the discussion line 147-151.

It would be useful to describe the title of the anti PR3.

We thank the reviewer for this interesting remark. Indirect immunofluorescence (IIF) for ANCA detection was performed using a commercial kit (Euroimmun®). Our patient had c-ANCA positivity with a titer of 1:40 (< 1:20). P-ANCA was negative. Positive serums for c- or p-ANCA at IIF are subsequently screened for antigenic specificity (MPO or PR3). Proteinase 3 antibody (anti-PR3) was positive by an immunodot technique (immunodot, Euroimmun®). Then we added in line 38, 39 “Our patient had c-ANCA positivity with a titer of 1:40 (< 1:20). P-ANCA was negative. Proteinase 3 antibody (anti-PR3) was positive by an immunodot technique”

The authors describe that tuberculosis was ruled out serologically, what type of test was used.

We thank the reviewer for this interesting remark. The QuantiFERON-TB Gold In-Tube (QFT-G) test for the diagnosis of tuberculosis disease was negative. We added this in line 37.

Competing Interests: No competing interests
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