Antiphospholipid syndrome, ferritin and fever: Hyperferritinemic syndrome, a nosological ally

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ABSTRACT

Hyperferritinemic syndrome represents a common nosological classification for systemic inflammatory syndromes, including catastrophic antiphospholipid syndrome, in which hyperferritinemia (> 500 ng/mL) is present. Recent studies suggest that in this syndrome, ferritin is more than a passive marker of inflammation, playing an active role in the process. We present the case of a 74-year-old female patient with elevated serum ferritin levels (above 1,000 ng/mL), along with an intense inflammatory syndrome, non-immune thrombotic microangiopathy, and multisystem involvement (pulmonary, cardiac, hepatic, pancreatic, neurological and renal changes), outlining the picture of a hyperferritinemic syndrome that is hard to classify otherwise. This underlines the necessity for diagnostic and classification criteria for this pathology.

Keywords: hyperferritinemic syndrome, catastrophic antiphospholipid syndrome (CAPS)

INTRODUCTION

The hyperferritinemic syndrome represents a common nosological classification for systemic inflammatory syndromes such as catastrophic antiphospholipid syndrome (CAPS), adult-onset Still's disease (AOSD), septic shock, multi-system inflammatory syndrome (MIS) of COVID-19, and hemophagocytic lymphohistiocytosis (HLH), including one of its acquired forms - macrophage activation syndrome (MAS) [1,2].

The hallmark of this new syndrome is, as its name suggests, the presence of hyperferritinemia, with a cutoff value equal to or greater than 500 ng/mL [2,3].

With the exception of mild to moderate AOSD, all of these five pathologies are acute life-threatening conditions that require fast diagnosis and treatment.

CAPS DIAGNOSIS

CAPS is a life-threatening complication of antiphospholipid syndrome (APS), with infection being the most common cause. The diagnostic criteria include histopathological confirmation of small-vessel occlusion, involvement of at least three organs, an antiphospholipid serological profile, and a rapid progression within days. Given the hyper-acute nature of this complication and the time required for both autoantibody testing and histopathological results, early diagnosis of CAPS is likely only for patients already known to have APS, with laboratory findings indicating non-immune thrombotic microangiopathy (as a substitute for histological evidence) [4].

SEPTIC SHOCK DIAGNOSIS

Sepsis represents an exaggerated acute systemic inflammatory response caused by an infection, most commonly associated with transient bacteremia. Since immediate treatment is crucial and confirming the infection can take time, empirical diagnosis and treatment are accepted. A qSOFA score (quick Sequential Organ Failure Assessment), a clinical screening score for sepsis, with two or more points along

with findings from the patient's medical history or physical examination suggesting infection, are sufficient for a sepsis diagnosis. Septic shock is a life-threatening condition that occurs in patients with sepsis that develops circulatory or metabolic dysfunction. The SOFA score is used as a prognostic score [5,6].

AOSD DIAGNOSIS

Like the majority of other collagen-vascular diseases, the need for standardized cases (referred to as 'classical' or 'typical' cases, so to speak) of AOSD for research purposes prompted the creation of classification criteria. The Yamaguchi criteria have now been replaced by the Fautrel criteria, with the strongest criterion being a value for glycosylated ferritin below 20%. With a specificity of 97.8% and an impressive increase of almost 50% in sensitivity compared to the Yamaguchi criteria, the Fautrel criteria can safely be used as diagnostic criteria [7]. The clinical findings (fever, skin changes, arthralgias, sore throat) and the blood count (leukocytosis with neutrophilia) are easily available, but in the absence of glycosylated ferritin, the nosological classification of this condition might prove difficult. AOSD is a diagnosis of exclusion [8].

MIS of COVID-19 DIAGNOSIS

CDC Case Definition for both MIS-A and MIS-C encompass clinical signs of at least 2 system involvement, fever, confirmation of COVID-19 exposure, systemic inflammation and cytopenia. CDC states that "...the patient should not have a more likely alternative diagnosis for the illness", making the MIS associated with COVID-19 a diagnosis of exclusion [9,10].

MAS DIAGNOSIS

The diagnostic criteria for HLH include clinical findings such as fever and splenomegaly and the para-clinical results consists in: cytopenia (at least 2 lineages affected), hypertriglyceridemia (>265 mg/dl), hypofibrinogenemia (<150 mg/dl), hyperferritinemia, hemophagocytosis in the bone marrow, spleen lymph nodes or liver, low or absent NK cell activity and elevated soluble CD25 or CXCL9 and. With the exception of the last two findings, which are not readily available, we can easily check 5 of the 8 required criteria. However in the absence of hemophagocytosis confirmation (that can take significant amount of time) the rest of the criteria are non-specific [11].

Recent studies show common clinical and laboratory findings:
- Hyperferritinemia;
- Hypercytokinemia;
- Infection as a trigger;
- Fever;
- Multiorgan involvement;
- Thrombocytopenia and anemia;
- Abnormal liver function tests;
- Coagulopathy;
- Elevated C reactive protein [1,2].

It is clear from the ongoing research that ferritin plays an active role in immunomodulation and is not solely a marker of inflammation [2,3,12]. The necessity for immediate treatment makes the hyperferritinemic syndrome a highly attractive nosological classification. This classification requires confirmation of systemic inflammation and hyperferritinemia, to which non-immune microangiopathic thrombocytopenia can be added. As new studies emerge and the role of ferritin in immunomodulation and the pathophysiology of these severe conditions becomes better understood, diagnostic criteria will be established [2,13–15].

CASE REPORT

We present the case of a 74-year-old female patient who has a known diagnosis of multifactorial thrombophilia (Primary APS, hyperhomocysteinemia, and Factor V Leiden), type 2 diabetes mellitus, and primary hyperaldosteronism due to bilateral adrenal adenoma. She is currently receiving oral anticoagulation (INR target 2-3), blood pressure control medication (spironolactone, perindopril, lercanidipine, and metoprolol), oral antidiabetic medication (metformin) and statin treatment. The patient was admitted to our hospital's emergency department with a fever (39° C), polymyalgia, productive cough and a confusional state.

Physical examination revealed mucocutaneous pallor, ecchymoses, tachypnea, prolonged expiration, bronchial rales, a Glasgow Coma Scale score of 10, and right hemiparesis.

Initial laboratory tests identified an inflammatory biological syndrome, hypoglycemia (32 mg/dL), moderate normocytic normochromic anemia (hemoglobin level of 10 g/dL), accompanied by moderate to severe thrombocytopenia (60,000/mL), neutrophilia (13,000/mL), and low titers of D-dimers (2.5 ng/mL). The INR (International Normalized Ratio) and rAPTT (activated partial thromboplastin time ratio) results were uninterpretable due to chronic oral anticoagulant treatment with VKAs (vitamin K antagonists) and, respectively, the presence of antiphospholipid syndrome.

The neurological evaluation and native brain CT examination (with reassessment at 24 hours) excluded a stroke. A careful medical history, with the help of the patient's relatives, revealed contacts with symptoms compatible with the diagnosis of Acute Upper
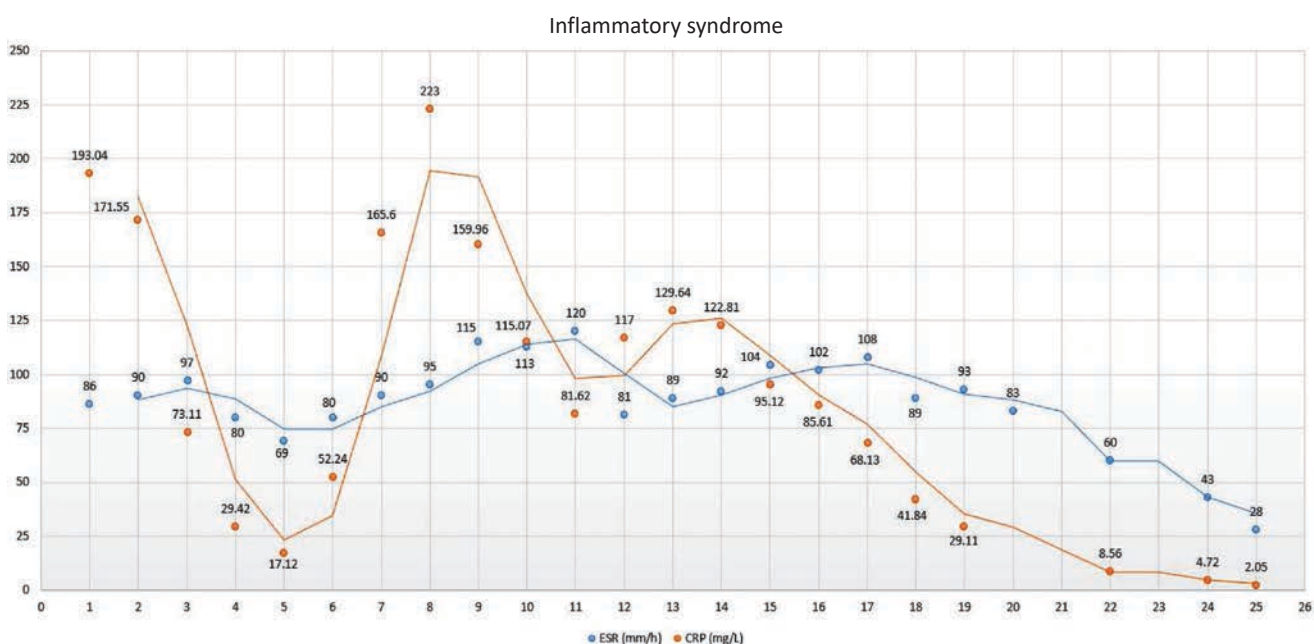
Inflammatory syndrome

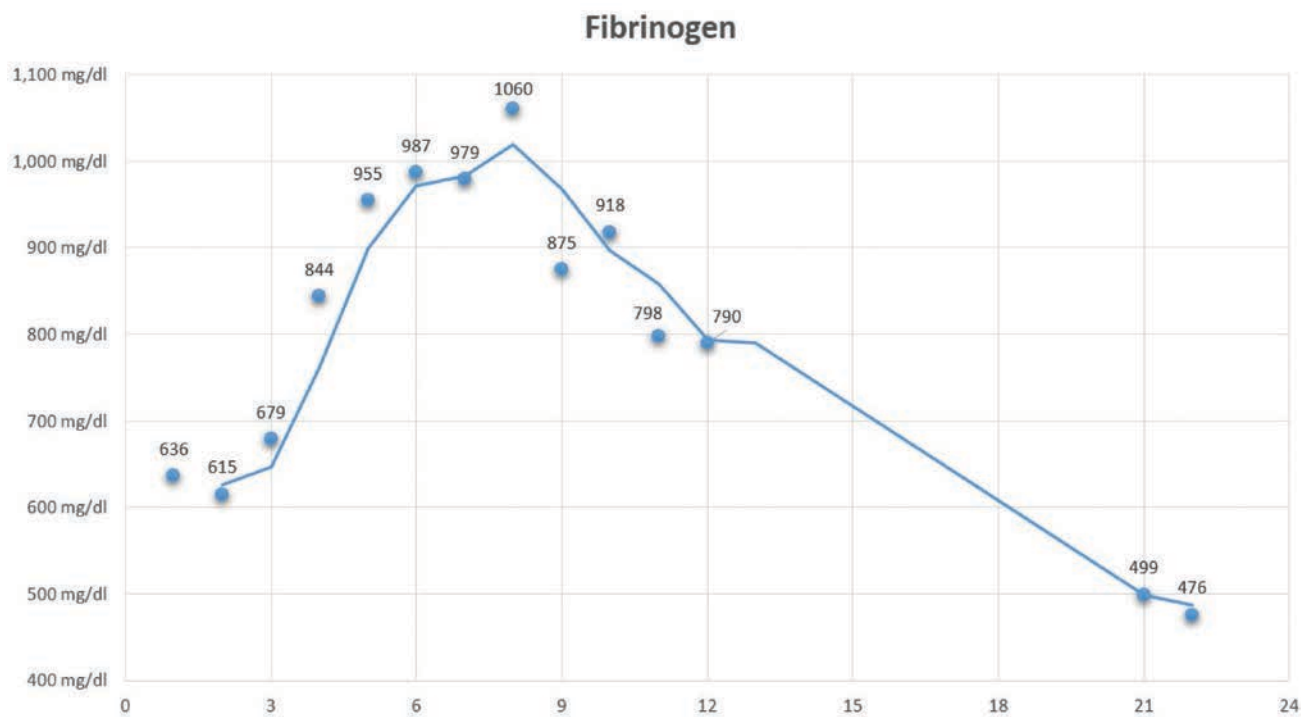**FIGURE 1** - Evolution of the inflammatory biological syndrome

Fibrinogen

FIGURE 2 - Evolution of fibrinogen values

Respiratory Tract Infection and the cause of hypoglycemia, which was self-administration of sulfonylureas (30 mg of gliclazide) following a high value recorded on a glucometer (above 250 mg/dL). After achieving euglycemia, the neurological signs showed a gradual improvement.

Taking into consideration the thrombocytopenia in a patient diagnosed with APS and a qSOFA score of 2, in association with the suspicion of pulmonary infection (superinfected viral lung infection), we initiated treatment for the highly probable sepsis. This involved parenteral antibiotic therapy, along with parenteral anticoagulation (Fondaparinux), and in-

travenous corticosteroid therapy (1mg/kg body weight).

The close follow-up evaluation revealed the subsequent laboratory results:
- negative rapid tests for COVID-19 and influenza, negative blood cultures, and inconclusive results for sputum analysis;
- procalcitonin above 5 ng/ml;
- marked inflammation (maximum value for CRP= 223 mg/L, ES = 120 mm/h, Fibrinogen= 1060 mg/dl), as see in Figure 1 and 2;
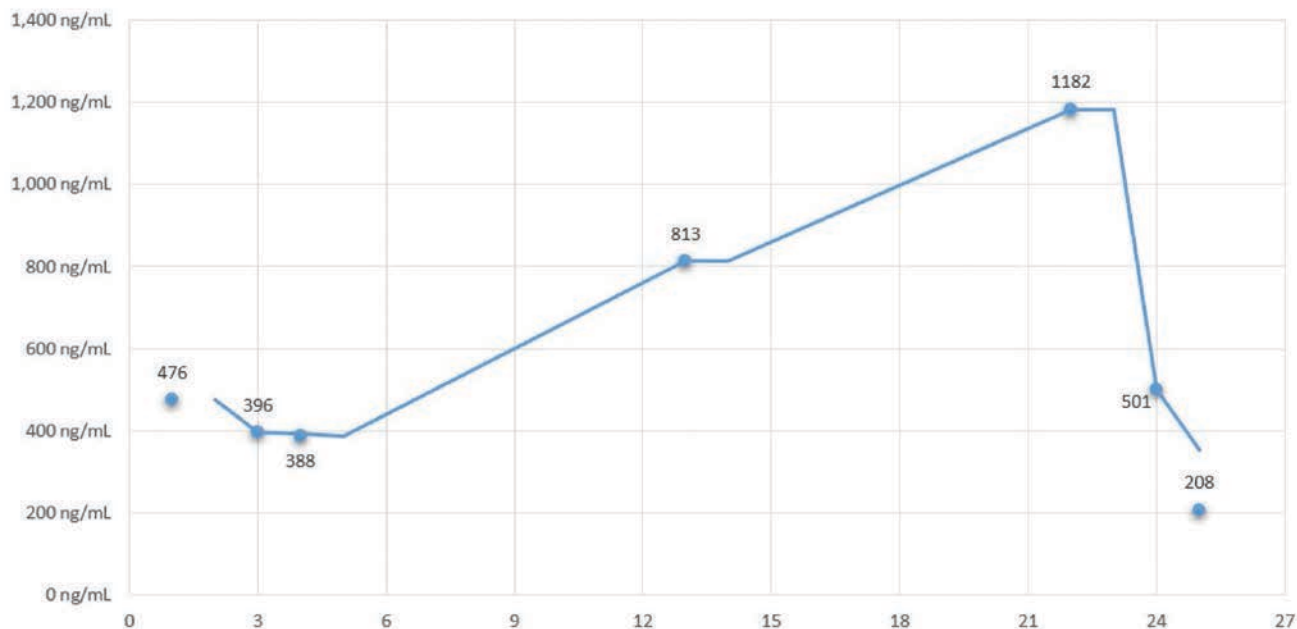- hyperferritinemia (maximum value of 1182 ng/mL) as seen in Figure 3;

Ferritinemia

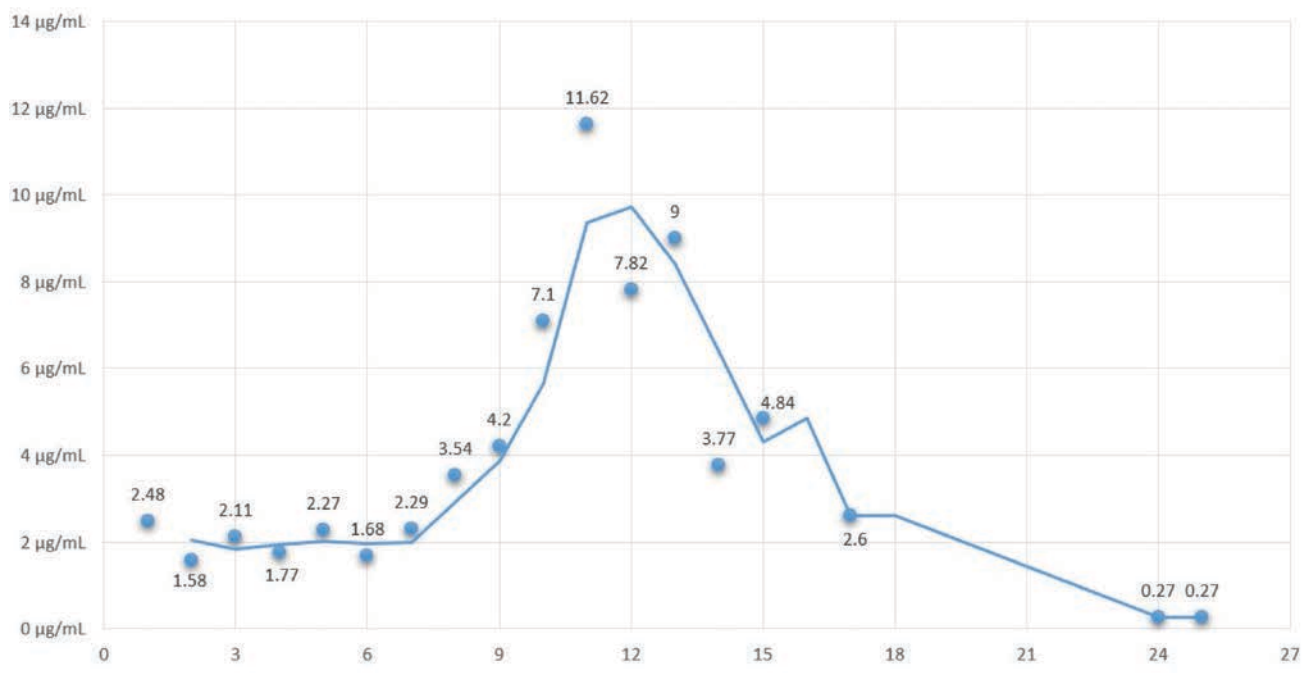**FIGURE 3** - Evolution of serum ferritin values

D-dimers

FIGURE 4 - Evolution of D-dimers values

- rising levels of D-dimers (maximum value of 11.2µg/mL), as seen in Figure 4;
- a slow rise in platelet and neutrophil count, as seen in Figures 5 and 6;
- a slow decline of hemoglobin, as seen in Figure 7;
- blood smear with schistocytes;
- negative Coombs test;
- high-risk antiphospholipid profile (positive lupus anticoagulant, with high positive beta2-glycoprotein I antibody titre).

Based on these findings, we considered the diagnosis of thrombotic microangiopathy (TMA) associated with a pulmonary infection (with an unknown etiological agent).

Over the following days, the patient remained stable with gradual favorable progression. However, she subsequently developed dyspnea, worsening cough, somnolence and retrosternal chest pain. Physical examination revealed pulmonary crackles and a progressive reduction in oxygen saturation. We promptly initiated a cardiologic and pneumological evaluation.
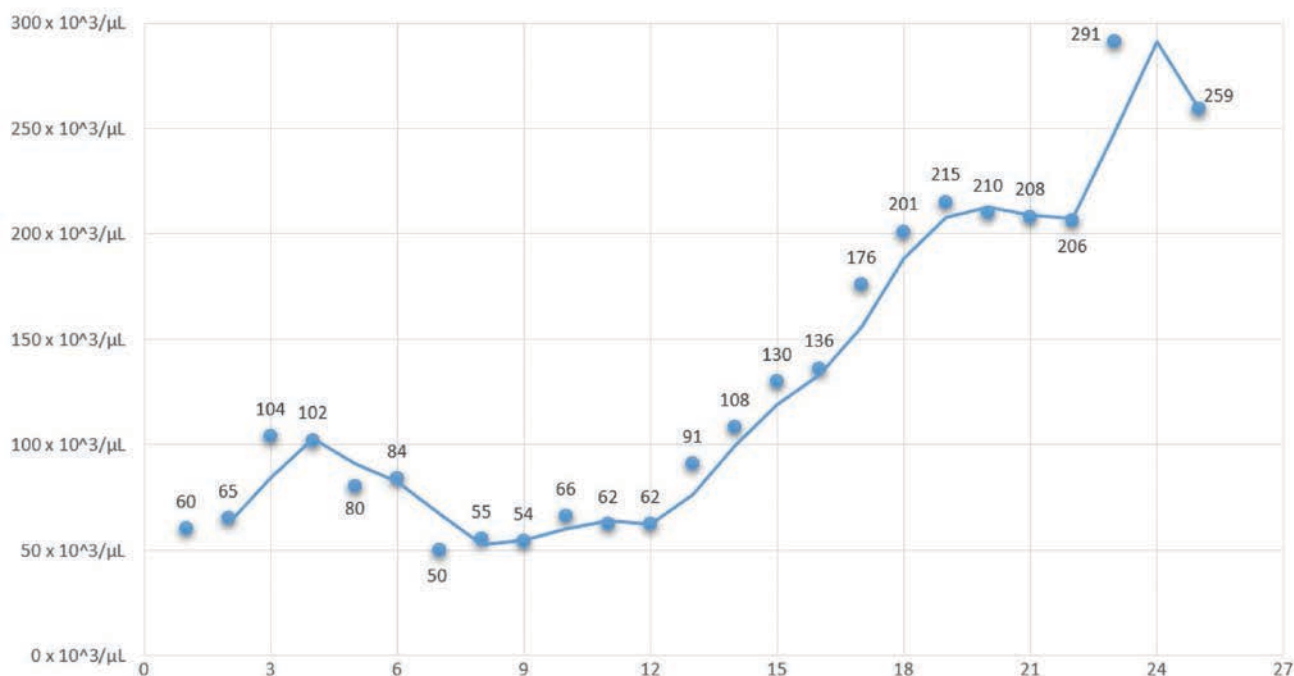
Platelet count

FIGURE 5 - Evolution of platelet number
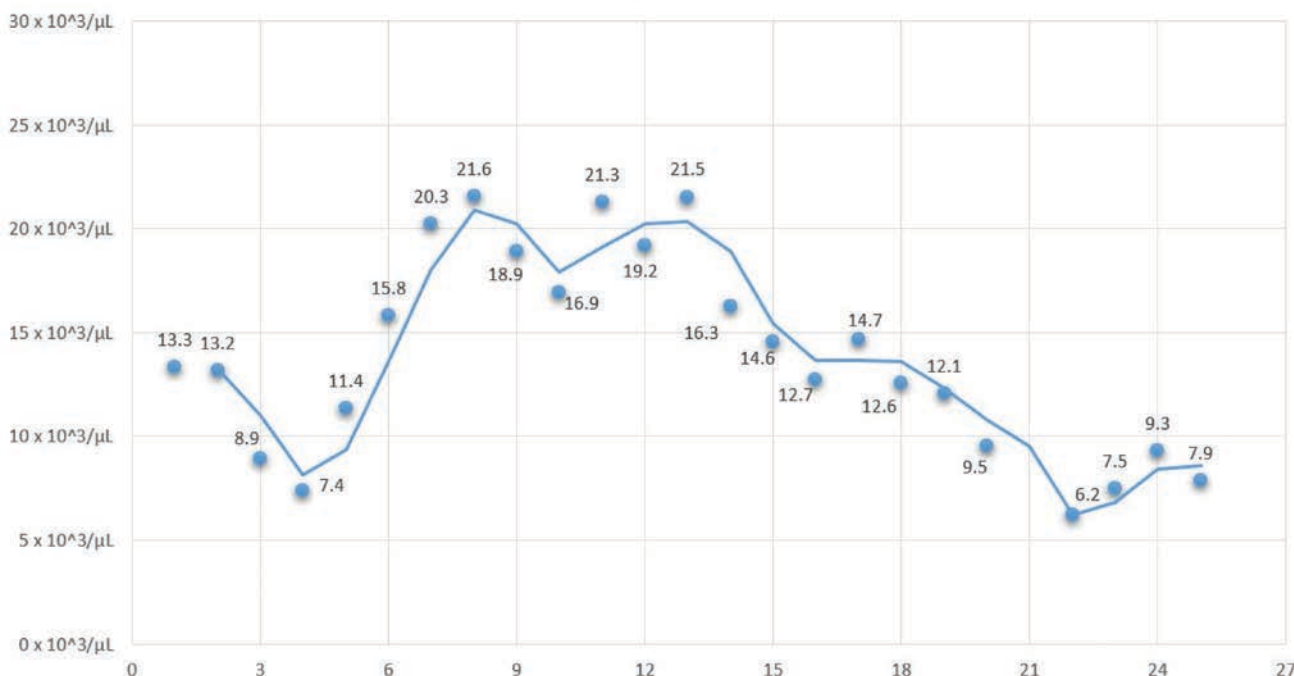
Neutrophil count

FIGURE 6 - Evolution of neutrophil numbers

A contrast-enhanced computed tomography (CT) of the thorax was performed, which revealed intraluminal filling defects and mild vascular enlargement of the pulmonary arteries. Additionally, bilateral peripheral ground-glass opacities and consolidations were observed, indicating 60% pulmonary involvement, as shown in Figure 8 and Figure 9. These findings were correlated with respiratory acidosis and an elevation in D-dimers value (Figure 4).

The pulmonary changes were consistent with the diagnosis of pulmonary thromboembolism (PTE) and COVID-like pneumonia (the RT-PCR test was negative).

The cardiological assessment consisted of:
- electrocardiogram (ECG) showing diffusely flattened T waves, otherwise unremarkable ECG;
- pro-brain natriuretic peptide (PRO-BNP) levels with a rising trend as shown in Figure 10;
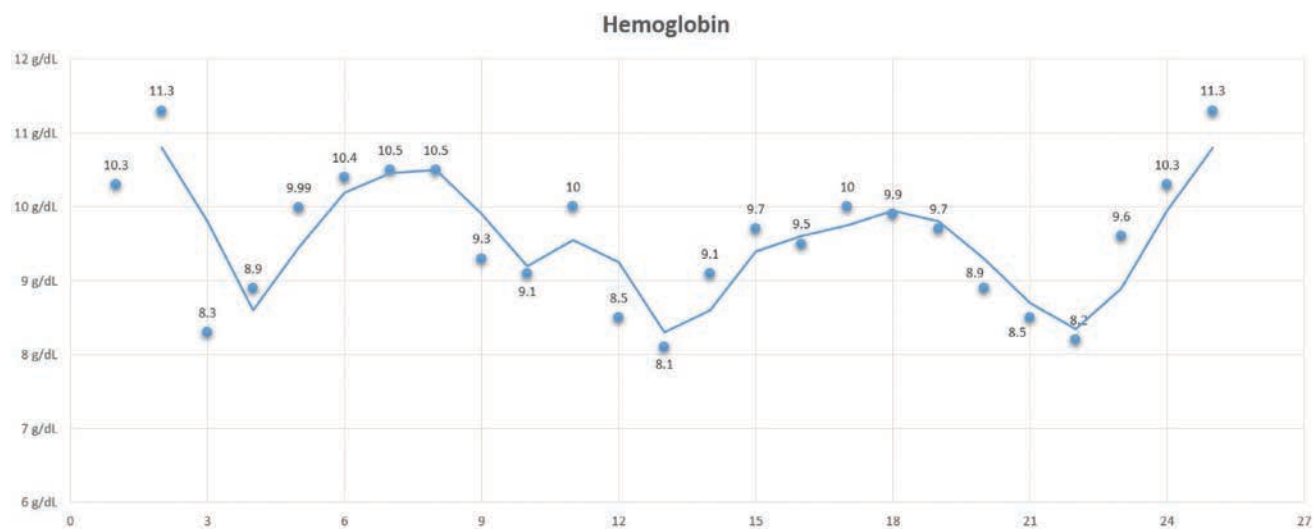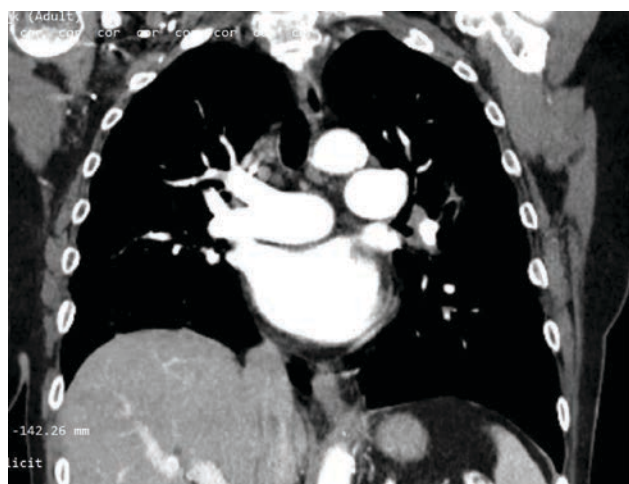
FIGURE 7 - Evolution of hemoglobin values

FIGURE 8 - Contrast-enhanced computed tomography scan (coronal thoracic section) reavealing PTE compatible changes
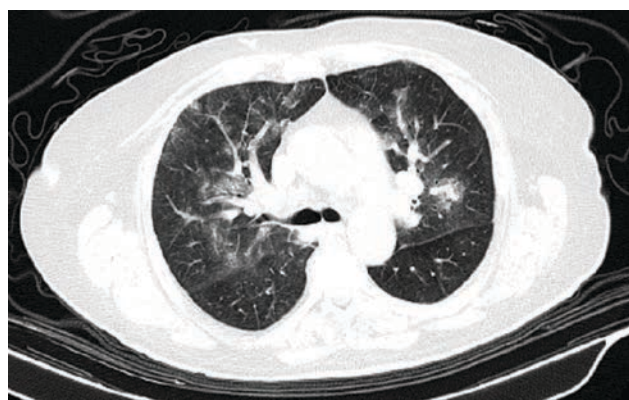

FIGURE 9 - Contrast-enhanced computed tomography scan (axial thoracic section) revealing COVID-like changes

- high-sensitivity troponin elevated values on a plateau;
- cardiac ultrasound showing global dyskinesia with a decreased ejection fraction of 40%.

The mild left ventricular systolic dysfunction was attributed to the highly probable viral myocarditis.

The hemodynamic impact of PTE was minimum (Pulmonary Arterial Systolic Pressure was normal). The treatment plan was adjusted to include oxygen therapy and the management of blood pressure and systemic congestion with loop diuretics.

The patient`s condition showed a gradual improvement with a significant amelioration in dyspnea and thoracic pain, decrease of pulmonary crakels, with normalization of EAB changes but with blood pressure maintaining systolic values above 165 mmHg and laboratory findings worsening as described in Figures 1-7.

In the subsequent period, the patient experienced epigastric pain with posterior radiation and pronounced nausea. There was an increase in the levels of liver cytolysis enzymes and pancreatic enzymes, which were previously within normal range. The maximum values observed were: AST elevated 11 times compared to the normal value (NV), ALT elevated 24 compared to times NV, amylase elevated 6.6 times compared to NV, and lipase elevated 4.3 times compared to NV, as depicted in Figures 11 and 12. Contrast-enhanced computed tomography scan of the abdomen was performed, the results describing an ill-defined heterogeneous areas throughout the liver, possibly ischemic (Figures 13 and 14).

Concurrently with all the changes described during hospitalization, renal function deteriorated as illustrated by a rise in serum creatinine as well as by the onset of hematuria associated with foamy urine and oliguria. This was initially consistent with stage I acute kidney injury, followed by rapid progressive renal function decline over the course of the next 3 weeks.

A Doppler ultrasound of the renal vessels was conducted, which excluded renal vein thrombosis. The patient did not experience hypovolemia, and the contrast-enhanced computed tomography scan of the abdomen did not show any signs of obstruction.
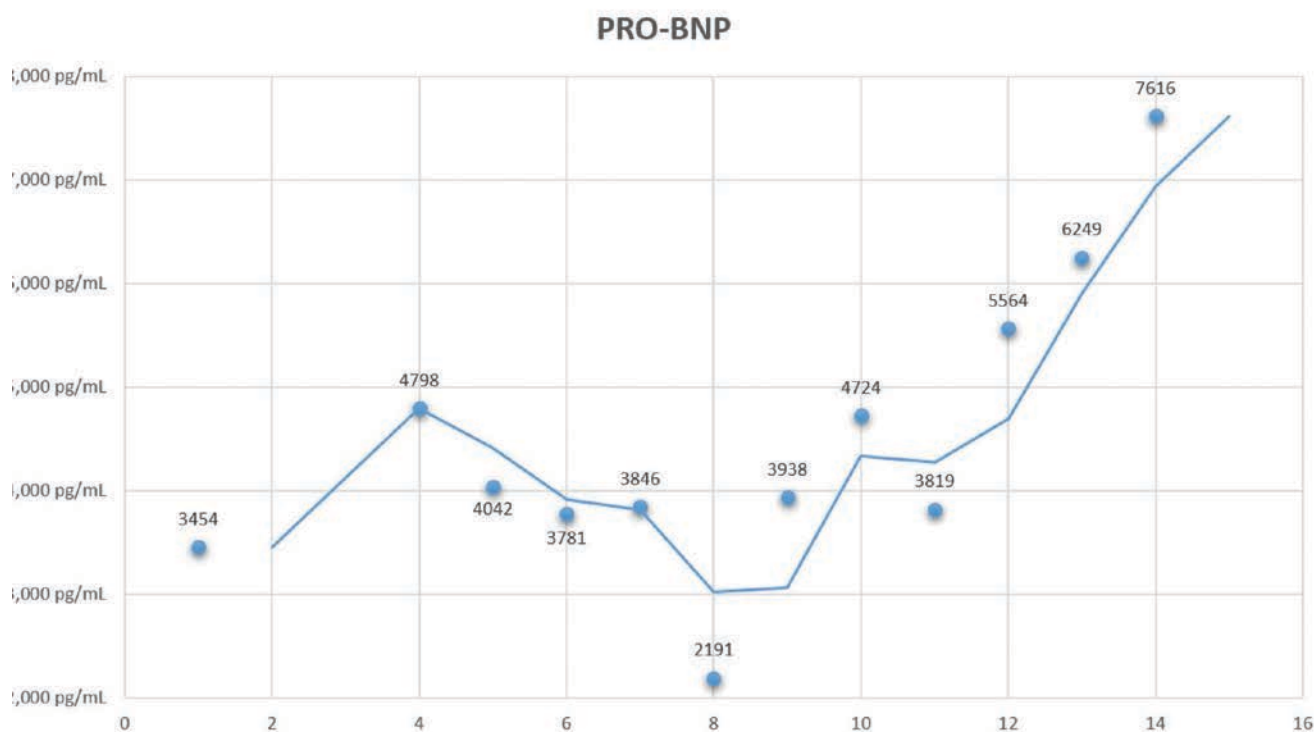
PRO-BNP

FIGURE 10 - Evolution of PRO-BNP values

Transaminases

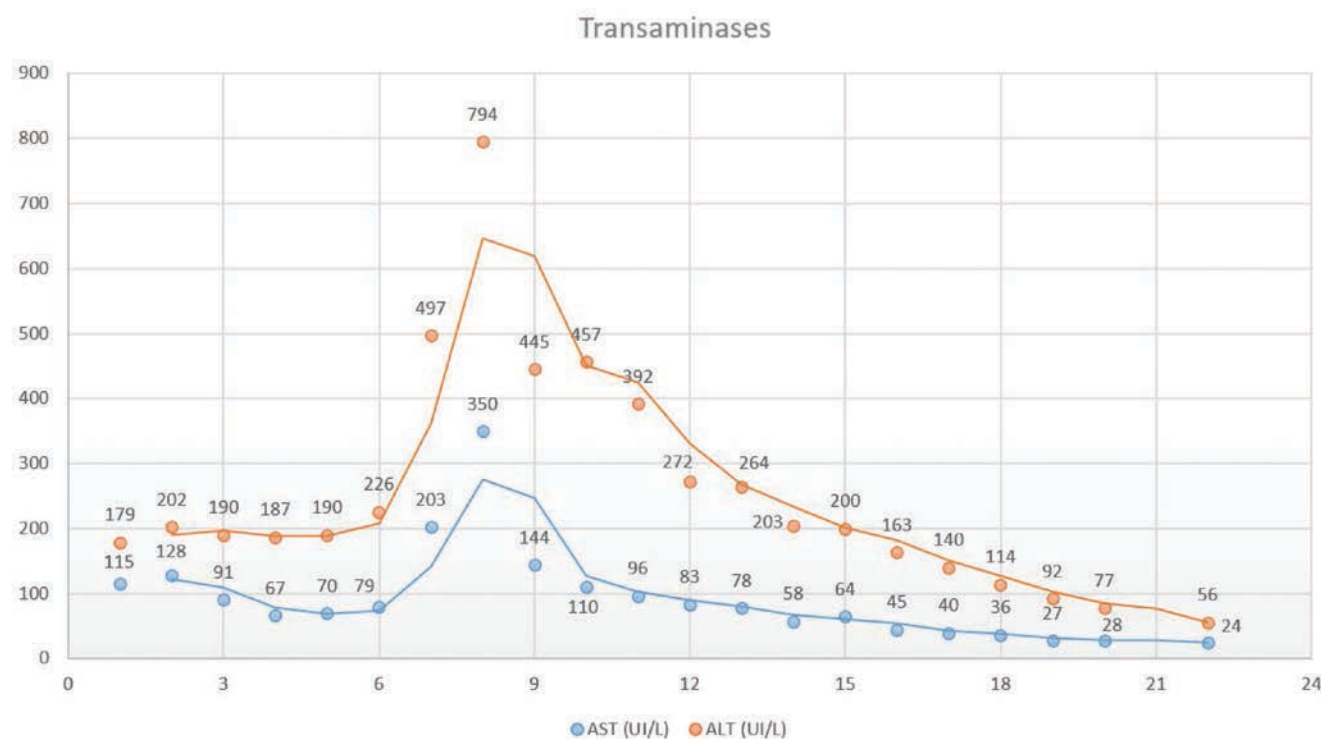○ AST (UI/L)   ○ ALT (UI/L)

FIGURE 11 - Evolution of transaminase values

Laboratory findings showed the onset nephrotic range proteinuria (as high as 4.76 g/24 h), as well as. The evolution of urinary volume/24 h, proteinuria/24 h, and serum creatinine are shown in Figure 15 (see next page).

Taking everything into consideration, we concluded that this was a rapidly progressive nephrotic-nephritic syndrome, most likely of a microangio-thrombotic cause.

The treatment plan was adjusted based on the new findings. Given the multi-etiological anemia resulting from microangiopathic hemolysis, renal loss, insufficient dietary intake, and severe infection, blood transfusions were administered (2 units of red blood cells, coinciding with the chronological minimum hemoglobin values described in Figure 7). Albumin supplementation was initiated to prevent hypovolemia and its complications. The presence of
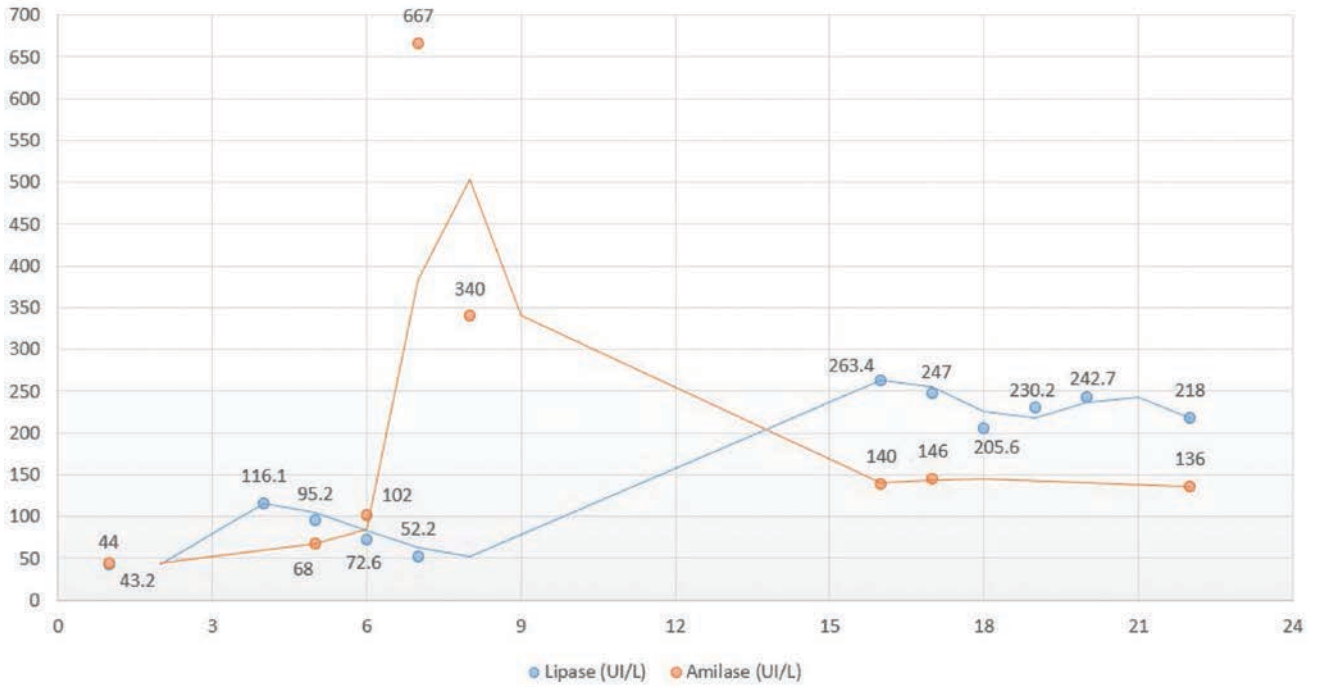
Pancreatic enzymes

FIGURE 12 - Evolution of pancreatic enzymes values

FIGURE 13 - Contrast-enhanced Computed Tomography scan (coronal section of the upper abdomen) revealing ill-defined, heterogeneous areas throughout the liver
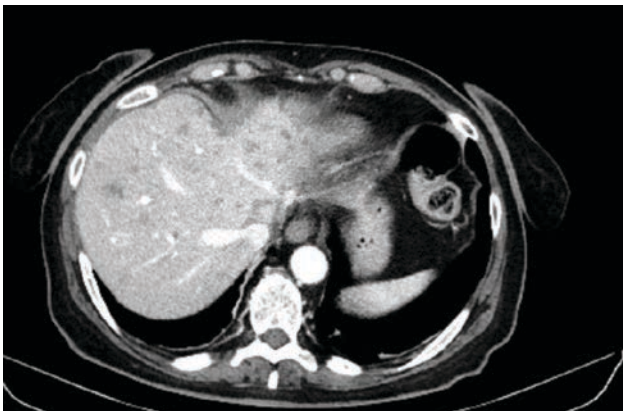

FIGURE 14 - Contrast-enhanced Computed Tomography scan (axial section of the upper abdomen) revealing ill-defined, heterogeneous areas throughout the liver
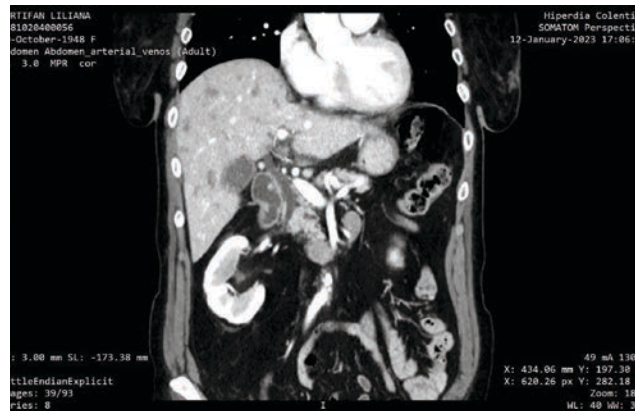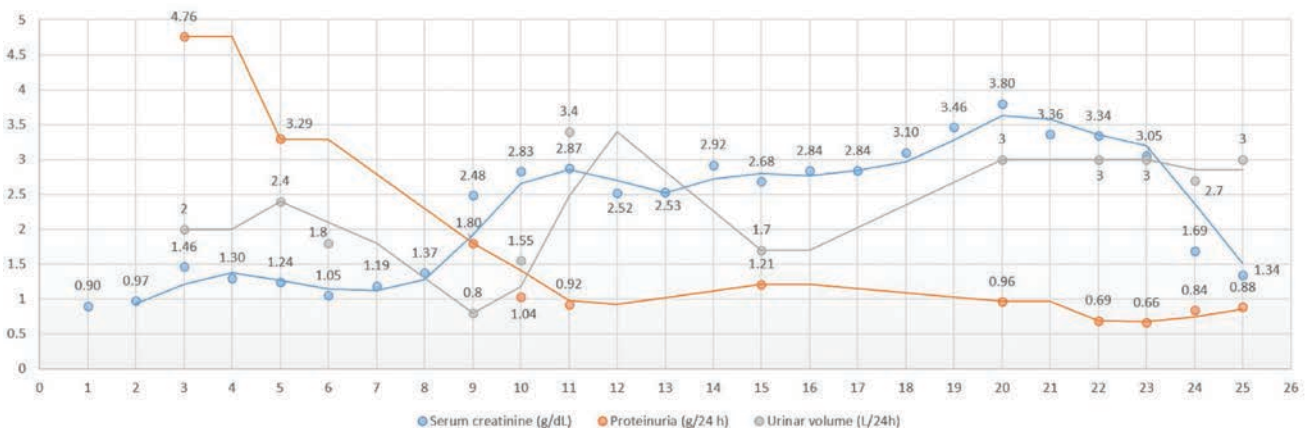
Renal function

FIGURE 15 - Evolution of serum creatinine, proteinuria and urinar volume values

pancreatitis necessitated dietary restrictions and pain management, although achieving effective pain relief was challenging due to the involvement of both the liver and kidneys.

Under our treatment, the patient showed gradual improvement in both clinical and paraclinical settings, with the partial exception of renal function. The patient underwent re-evaluation at 2 weeks after discharge, as well as at three and six months. Despite the overall improvement, significant renal sequelae persisted: a decrease in estimated glomerular filtration rate (eGFR) from 67 ml/min/1.73 m² at the time of admission to the current level of 42 ml/min/1.73 m² at 6 months after hospital discharge, residual proteinuria ranging from 0.5 to 1 g/24h.

DISCUSSIONS

The case presented illustrates the difficulty of a satisfying diagnosis in a patient with a life-threatening condition.

The consistently elevated fibrinogen levels, non-autoimmune hemolytic anemia, and maintenance of platelet count around 60,000/µL, with a PLASMIC score of 4 (excluding the prolonged coagulation tests for the reasons mentioned before) in a patient with primary antiphospholipid syndrome, rendered the diagnosis of disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP) improbable. Instead, considering the clinical presentation and the aforementioned factors, catastrophic sntiphospholipid syndrome (CAPS) emerged as a strong possibility [16]. We used Fondaparinux as the parenteral anticoagulant of choice in the unlikely case heparin-induced thrombocytopenia (HIT) overlap [17].

Elevated serum ferritin levels (above 1000 ng/mL) along with intense inflammatory syndrome and multi system involvement (pulmonary, cardiac, hepatic, pancreatic, neurological and renal changes) outline the picture of a hyperferritinemic syndrome difficult to classify otherwise, the particularity in this case [1,2].

We were unable to confirm the suspected final diagnosis of CAPS (catastrophic antiphospholipid syndrome) as the infection-triggered thrombotic microangiopathy (TMA) due to the lack of histopathological data, mainly because obtaining tissue samples posed a high risk of bleeding [4]. Macrophage activation syndrome (MAS) was deemed improbable in this case as the triglyceride values were normal and the fibrinogen values were high. Additionally, apart from the nonspecific fever, there was no clinical suspicion for adult-onset Still's disease (AOSD) [2]. COVID-19-associated multi-system inflammatory syndrome (MIS-A) was indeed considered as a potential diagnosis, given the hyperferritinemia and multi-system involvement. However, the cardiac involvement in this case was mild, and there was no confirmation of a COVID-19 infection. As for the last hyperferritinemic syndrome, septic shock, we couldn't identify any microbe, the patient was never hypovolemic, hypotensive or had metabolic acidosis, the infectious acting more like a trigger than a principal pathological mechanism. The presented case reiterates the fact that infection is the most common cause of triggering a hyperferittinemic syndrome [6,9].

Given the patient's age, along with the associated comorbidities, notably the long history of hypertension and diabetes mellitus, it is entirely possible that there was a degree of glomerular sclerosis and/or basal membrane thickening prior to her presenting in the clinic.

In this case, compared to previously healthy individuals, the patient was more susceptible to not only acute kidney injury, but also to poorer likelihood of nephron recovery after the initial lesion. The 'thrombotic storm' most likely broke the fragile tissue homeostasis, resulting in a more severe injury, only partial recovery and a significant permanent decline in renal function, which was observed during the reevaluations [18,19].

Methylprednisone, plasma exchange, and intravenous immunoglobulin (IVIG) are effective treatments for these pathologies. However, among these options, corticosteroid therapy is the only readily available one [1,2]. Without a clear diagnosis, we were unable to initiate IVIG or plasmapheresis. The patient's condition remained consistently on the borderline of decompensation; however, she never met the criteria for admission to the intensive care unit.

The nosological classification of this case as a hyperferritinemic syndrome, with appropriate staging of severity and initiation of a more aggressive treatment such as IVIG or plasma exchange, might have proven to be more cost-efficient, resulting in fewer hospitalization days and prevention of permanent renal sequelae.

CONCLUSION

The confusional syndrome associated with tachypnea in the context of bacteriemia with systemic inflammatory repercussions suggests the onset of sepsis, which triggered a microangiopathic thrombotic syndrome. The patient did not meet sufficient criteria for any specific hyperferritinemic syndromes, nor for conditions such as TTP, HIT, and DIC.

The renal prognosis in this case is negatively impacted by the current degree of glomerulosclerosis, consistent with stage G3bA3 chronic kidney disease (CKD), making it even more important that the risk factors for further renal function decline are avoided or properly managed. Of those we'd like to mention blood pressure and diabetes mellitus control and especially the reduction of the residual proteinuria to a

minimum. Additionally, subsequent acute kidney injuries, regardless of their cause, would only add to the vicious cycle described above [18].

To summarize, this case highlights the significance of conducting further studies to establish a clear nosological classification of hyperferritinemic syndromes. Unfortunately, for this to happen, time and extensive research is needed, but hopefully, at some point, the clinician`s arsenal will include diagnostic and classification criteria for this pathology.

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