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SCIENTIFIC LETTER

Myocardial involvement in eosinophilic granulomatosis with polyangiitis: a multimodal approach

Afectación miocárdica en la granulomatosis eosinofílica con poliangitis: un abordaje multimodal

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Introduction

Almost 7 million patients with chest discomfort present to emergency department in United States every year and differential diagnosis includes a broad spectrum of pathologies, being up to 20% of cardiovascular cause, and up to 5.5% of these are life-threatening conditions[1]. Differential diagnosis board should include other causes besides acute coronary syndrome.

Systemic vasculitides are classified in order of affected vessel size (large, medium, or small vessel)[2,3]. Heart involvement is related to a worst prognosis[4] and could be affected on almost all type of vasculitides[2], especially on medium vessel and small vessel (Eosinophilic granulomatosis with polyangiitis [EGPA] and granulomatosis with polyangiitis [GPA], which are part of the ANCA associated vasculitis). Even though EGPA is less prevalent than GPA, heart is more frequently affected on the first one[4]. This paper presents the case of a young female patient with fever, chest pain, and cough with a systemic vasculitis as the cause of myocardial damage.

Case report

A 43-year-old woman with asthma is admitted due to fever and productive cough associated to fatigue, dyspnea, and a 5 kg unintentional weight loss. She also had several episodes of oppressive chest pain related to exercise that quickly disappeared with rest. The chest X-ray showed a bilateral upper lobe consolidation and a right lung nodular lesion (Fig. 1A). The electrocardiogram (ECG) was normal, complete blood count showed leukocytosis with eosinophilia, and the urine antigen for *Streptococcus pneumoniae* was positive.

The patient had no known cardiovascular risk factors or toxic habits, nor family history of cardiovascular or autoimmune disease. Her only past medical history was mild persistent asthma controlled with formoterol/beclomethasone inhalators. She was hemodynamically stable and febrile (tympanic temperature 38.3 degrees Celsius). Pulmonary auscultation showed bilateral upper lobe rales. Cardiac, abdominal, and neurologic examination were unremarkable. She had violet skin lesions and subungual hemorrhages on some of her fingers and toes (Fig. 1B and C).

During hospitalization, she presented oppressive chest pain irradiated to left shoulder, associated to nausea and diaphoresis. An ECG was performed with changes suggestive of multi-vessel disease/diffuse ischemia (Fig. 1D), but chest pain spontaneously disappeared in < 10 min and a second ECG was normal.

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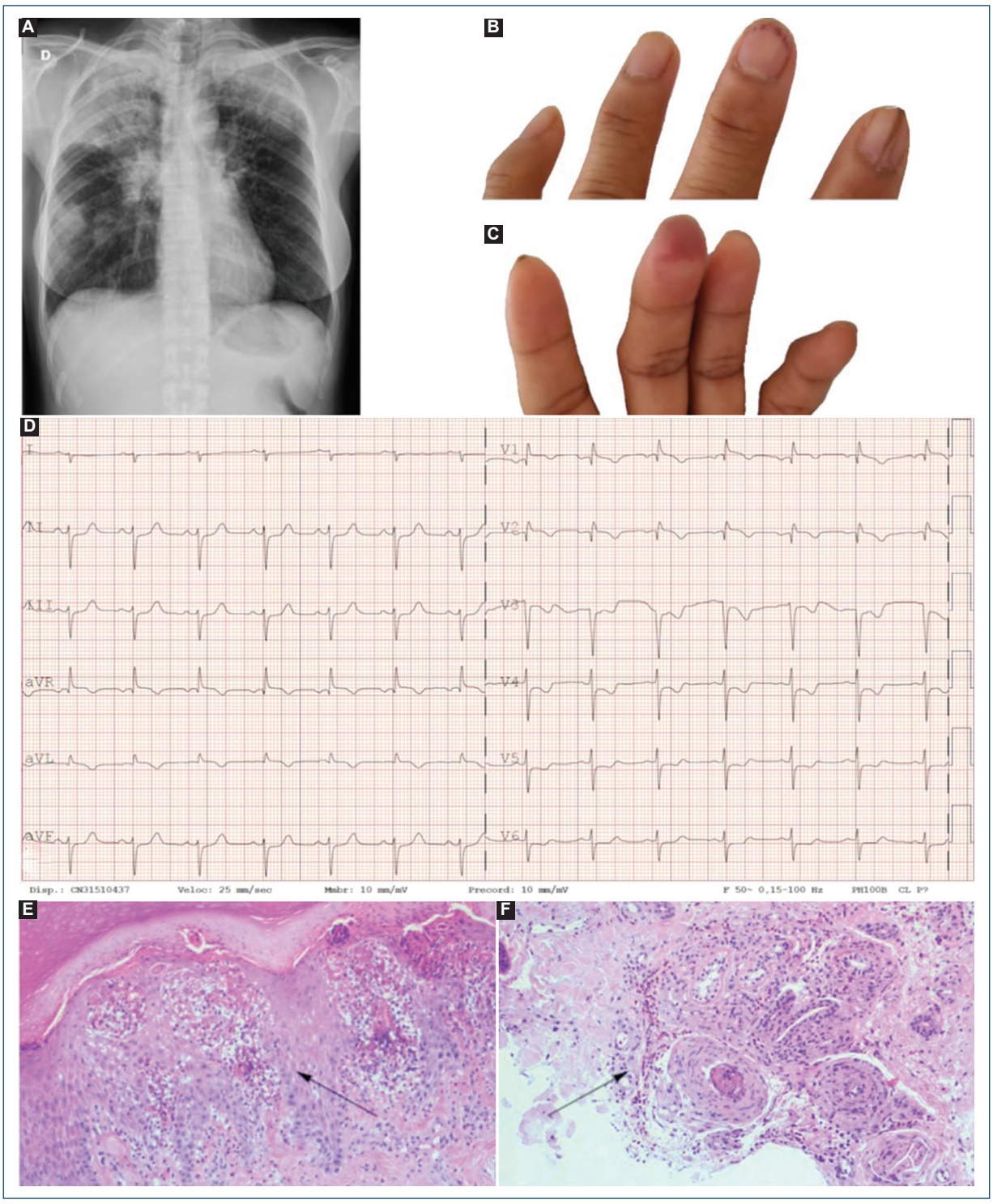

Figure 1. A: chest X-ray that shows bilateral upper lobes and right parahiliar and medium lobe infiltrates. **B:** organized subungual hemorrhage is found on the third finger. **C:** nodular violet lesions could be found in fingers and toes. **D:** twelve-lead ECG during chest pain episode that shows incomplete right bundle branch block with a ST segment depression > 1 mV in more than 6 anterior an inferior leads, with a ST segment elevation > 1 mm in V1 and aVR, suggestive of diffuse ischemia. **D** and **E:** microphotographs on H&E. **E:** skin biopsy with abundant eosinophils on superficial dermis with epidermic infiltration causing hyperplasia, acanthosis, spongiosis, hyperkeratosis with parakeratosis, and intraepidermal vesicles. **F:** reticular dermis showing intravascular and perivascular eosinophilic infiltration with discrete involvement of the vascular wall. Early stages of fibrinoid necrosis can be observed.

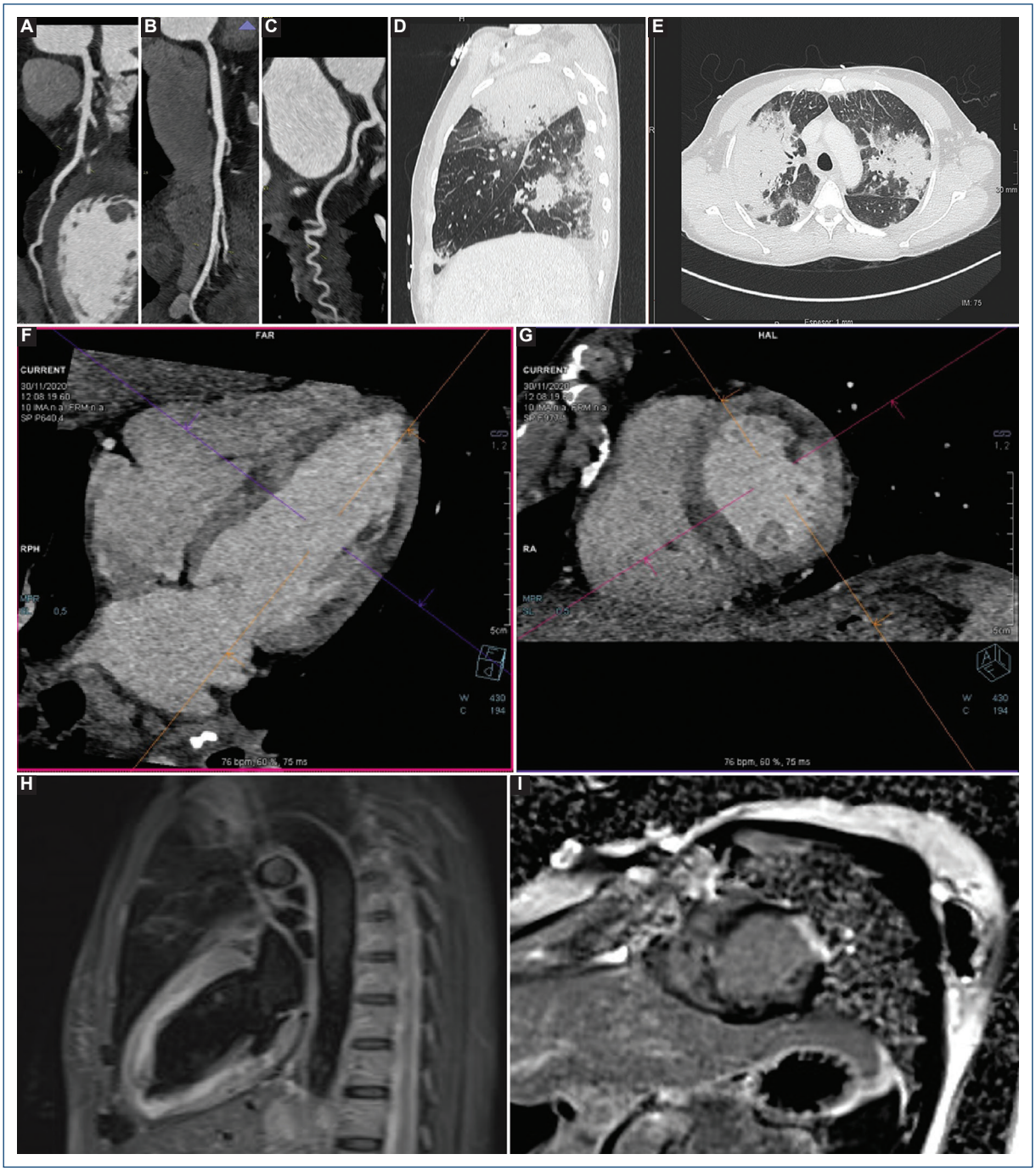

Figure 2. Coronary computed tomography-scan angiography showed no lesions on epicardial coronary arteries. **A-C:** curved planar reconstruction of left anterior descendent, right, and circumflex coronary arteries are shown. **D** and **E:** bilateral pulmonary dense opacities and bilateral hilar and mediastinal lymphadenopathies. **F and G:** four chamber and short axis at papillary muscles views on venous phase in which patchy hypoenhancement areas with no coronary distribution can be appreciated, suggestive of small vessels vasculopathy. Cardiac magnetic resonance showing akinesia and thinning of the middle anterolateral and apical anterior segments. **H** and **I:** hypokinesia of the middle septum. Areas of edema and transmural subendocardial late gadolinium enhancement (LGE) in the middle anterolateral segments and a focus of intramyocardial LGE in the middle septal-inferior segment.

An emergent echocardiography showed a normal size and thickness left ventricle with an ejection fraction of 58%, with hypokinesia of anterior basal segment and medium inferoseptal segment. Right ventricular and valvular function was preserved. Ultrasensitive Troponin T and eosinophils were on continuous elevation on seriation (with peak of 763 ng/L and 16.1 × 10^3, respectively). An urgent coronary CT-Scan angiography (CCTA) was performed that showed no lesions on epicardial coronary arteries (curved planar reconstruction of the left anterior descendent, right and circumflex coronary arteries are shown on Fig. 2A-C, respectively), but patchy areas of subendocardial hypoenhancement on venous phase and regional myocardial hypokinesia without coronary distribution associated with bilateral pulmonary dense opacities (upper lobes and right medium lobe) and bilateral hilar and mediastinal lymphadenopathies (Fig. 2D and F). These findings were suggestive of small-vessel necrotic vasculitis that associated to hypereosinophilia make EGPA (formerly called Churg-Strauss vasculitis) as the first diagnostic possibility. A cardiac magnetic resonance (CMR) showed left ventricle mild systolic dysfunction (ejection fraction 53%) with findings suggestive of ischemic etiology such as akinesia and thinning of the anterolateral and apical anterior segments associated to subendocardial late gadolinium enhancement on those segments (Fig. 2H and I).

Antibodies for autoimmune disorders were negative (including the peripheral-antineutrophil cytoplasmic antibodies) with an Immunoglobulin E elevation and mildly elevated Immunoglobulin G (IgG), due to elevation of the IgG4 subfraction (4.4 g/dL, normal range 0.05-1.2). Biopsies of the skin finger lesion, pulmonary upper lobe infiltrate (CT-Scan-guided thick needle), and a nasal mucosa were performed. Skin (Fig. 1E and F), nasal concha, and lung biopsies showed eosinophilic infiltration confirming the main diagnostic suspicion of EGPA, as the patient met Lanham's criteria and American College of Rheumatology criteria of 1990[5].

Once completed the three doses of methylprednisolone 250 mg, prednisone 1 mg/Kg was initiated, and 4 days later, cyclophosphamide was associated to corticoids. The patient was clinically asymptomatic, normalized eosinophil count and cardiac biomarkers. Dose was downtitrated as outpatient without recurrence at 1 year.

Discussion

For patients with chest pain and elevation of MDB but with low pretest probability of atherosclerotic cardiovascular disease, CCTA could be used as an alternative to invasive coronary angiography.

In this patient, the clinical presentation, imaging techniques, and tissular biopsy allowed to stablish a final diagnosis of a systemic vasculitis. EGPA is one of the less common vasculitides with a prevalence of 10.7-13 cases/million inhabitants and although is classified as an ANCA associated vasculitis, < 30% of patients with this disease and heart involvement test positive for these antibodies[3]. The patient, on this case report, tested negative for ANCA antibodies but had a significant elevation of IgG4. It has been previously described the association of EGPA to serum IgG4 elevation and recently associated as a possibly overlap syndrome[5] between IgG4 related disease and EGPA.

In these patients, extracardiac manifestations were related to eosinophilic pneumonia, subungual hemorrhage, and violet nodular skin lesions on fingers. Cardiac manifestations were mainly ischemic heart disease (associated to ECG changes suggestive of multi-vessel disease due to patchy microangiopatic vasculopathy rather than epicardial coronary disease), and possible eosinophilic myocarditis, described as focus intramyocardial LGE. Endomyocardial biopsy was not performed because eosinophilic tissue infiltration was documented on other organs and its presence on myocardial tissue would not change the therapeutic approach. As shown on this case, heart could be affected in many ways in patients with EGPA, being heart failure, pericardial effusion, chest pain, and myocarditis the most frequent findings[6]. In a series of patients with EGPA, 31% of deaths were attributed to cardiac causes[7].

The mainstay treatment for EGPA is corticosteroids, but relapses are frequent. In patients with 65 years or older, renal failure, associated cardiomyopathy, or gastrointestinal involvement, corticosteroids must be started at high doses followed by an induction regimen of cyclophosphamide for 3-6 months associated to oral corticosteroids. Rituximab has been used with good results, especially when the patient has high IgG4[5]. Prognosis has improved with the use of corticosteroids and immunosuppressants, with 5-year survival rate of 10% in 1990 to 90% on 2018[7].

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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