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CLINICAL COMMUNICATION

An atypical caseof Churg–Strauss syndrome

Un caso atípico de síndrome Churg-Strauss

M. Fernández García[a,*], C. Lage[a], E. Monfá[b], J.J. Gómez[c], C. Valero[a]

[a] Service of Internal Medicine, University Hospital Marqués de Valdecilla, University of Cantabria, IDIVAL, Santander, Spain
[b] Service of Nephrology, University Hospital Marqués de Valdecilla, University of Cantabria, IDIVAL, Santander, Spain
[c] Department of Anatomic Pathology, University Hospital Marqués de Valdecilla, University of Cantabria, IDIVAL, Santander, Spain

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Introduction

Churg–Strauss syndrome (CSS), also known as allergic granulomatosis angiitis and recently as eosinophilic granulomatosis with polyangiitis (EGPA), is characterized by the presence of vasculitis, necrotizing extravascular granuloma and eosinophilic infiltration, although these three histopathological features rarely coincide, least of all in the same tissue sample.[1] It is classified as a small and medium-vessel vasculitis and associated with anti-neutrophil cytoplasmic antibodies (ANCA), although *vasculitic involvement* may be absent during early stages. The exact etiology of CSS is unknown but its pathogenesis includes an autoimmune etiology with an alteration of cell and humoral immunity.[2] The renal involvement has not been considered as one of its distinctive features, yet it may be more frequent and relevant than previously thought. Besides, other manifestations, even less frequent, may be present in EGPA patients.

We report the first case of a female patient diagnosed with ANCA-negative CSS with renal involvement in the form of eosinophilic interstitial nephritis who developed a case of severe cholestatic hepatitis following azathioprine therapy. We think that all of these features make our report a case of special interest to the internist.

Case report

A 62-year-old housewife, with no environmental exposure to toxic substances or airborne allergens, diagnosed with bronchial asthma a year ago, was first admitted to the emergency department after one week of dyspnea and fever up to 39 °C. Her treatment included fluticasone/salmeterol. Pulmonar auscultation revealed slight crackles in the left hemithorax. Laboratory findings showed 11,000 leukocytes (11% eosinophils). Chest X-rays showed a peripheral condensation in left lung, so amoxicillin–clavulanate was prescribed. She was re-examined 10 days later but the same symptoms persisted. The follow-up chest-X rays revealed multiple bilateral pulmonary infiltrates. Re-questioned, she referred a 1 month and a half history of anosmia, asthenia, unquantified weight loss and generalized myalgias so she was admitted to our department for further studies. Her temperature was 38.6 °C and a striking rhinolalia, lasting for a month, was present. The remainder of the physical examination was unremarkable. Lab results at this time showed 14,000 leukocytes (22% eosinophils; 2940 cells/μL), an ESR of 138 mm/h. Glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) and bilirubin were normal

* Corresponding author.
E-mail address: magdafergar@yahoo.es (M. Fernández García).

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(GGT 40 U/L, AST 24 U/L, ALT 22 U/L, AP 84 U/L, bilirubin 0.3 mg/dL). Urine sediment analysis results showed microscopic hematuria (++++), a large number of red blood cells (60/high power field, 50% dysmorphic), 700 mg proteinuria in 24-h urine, creatinine clearance >60 mL/min) and mild leukocyturia with 20 white blood cells/high power field (WBC/HPF).

The CT scan showed multiple peripheral pulmonary infiltrates with air bronchogram, multiple mediastinal and bilateral hilar lymphadenopathy (Fig. 1, panel a) with an increased uptake in the positron emission tomography (PET). Paranasal sinuses X-ray revealed mucosal thickening, reduced air intake in both maxillary sinuses and a level in right maxilar sinus. All the microbiological results (including tuberculin test) were negative. Angiotensin-converting enzyme (ACE) was negative too. Immunological serum tests (rheumatoid factor, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies anti-proteinase 3 and anti-myeloperoxidase, anti-glomerular basement membrane, complement) only revealed an IgE value of 323 IU/mL (normal range: 0.0–1000 IU/mL). Bronchoalveolar lavage (BAL) showed 35% eosinophils and negative for malignant cells. An endobronchial ultrasound could not be performed due to an episode of psychomotor agitation while undergoing the fibroscopy. In order to establish a histopathological diagnosis, a renal biopsy was performed. Renal histology showed focal segmental lesions with mesangial proliferation (Fig. 1, panel b), active lesions with inflammatory cells and tubulointerstitial nephritis with massive infiltration of eosinophils, including eosinophilic microabscess formations (Fig. 1, panel c). Immunofluorescence showed no immune deposits. CSS was established based on the presence of asthma, eosinophilia, lung infiltrates, sinusitis, and renal histological findings.

After starting treatment with oral prednisone (0.75 mg/kg/day) clinical and X-ray results improved rapidly (Fig. 1, panel d). One month later, microscopic hematuria (++), proteinuria (380 mg/24) and mild leukocyturia (10–15 WBC/HPF) persisted so we added azathioprine (100 mg/day) after the dosage of thiopurine methyltransferase (TPMT) activity in order to prevent any potential toxicity. The mutant alleles, associated with about 95% low or reduced enzymatic activity, were absent. Three weeks later, the patient presented episodes of vomiting and nausea. Lab tests revealed a severe cholestatic hepatitis (GGT 799 U/L, ALT 555 U/L, AST 314 U/L, AP 350 U/L, bilirubin 1.3 mg/dL), so azathioprine (AZA) was immediately stopped and other causes of liver injury were ruled out. During follow-up, liver function tests became normal. She is now on a daily maintenance dose of 5 mg prednisone and only mild microhematuria (+) persists.

Discussion

CSS is characterized by the coexistence of at least four out of the six criteria proposed by the American College of Rheumatology (asthma, eosinophilia, neuropathy, lung infiltrates, paranasal sinus alterations and extravascular eosinophilic infiltrations) with a 85% sensitivity and 99.7% specificity for the identification of the disease.[1] The clinical expression is a multisystem disorder whose presentation can be quite variable.

Peripheral blood eosinophilia is the most characteristic finding. Different cytokines and chemokines produced by

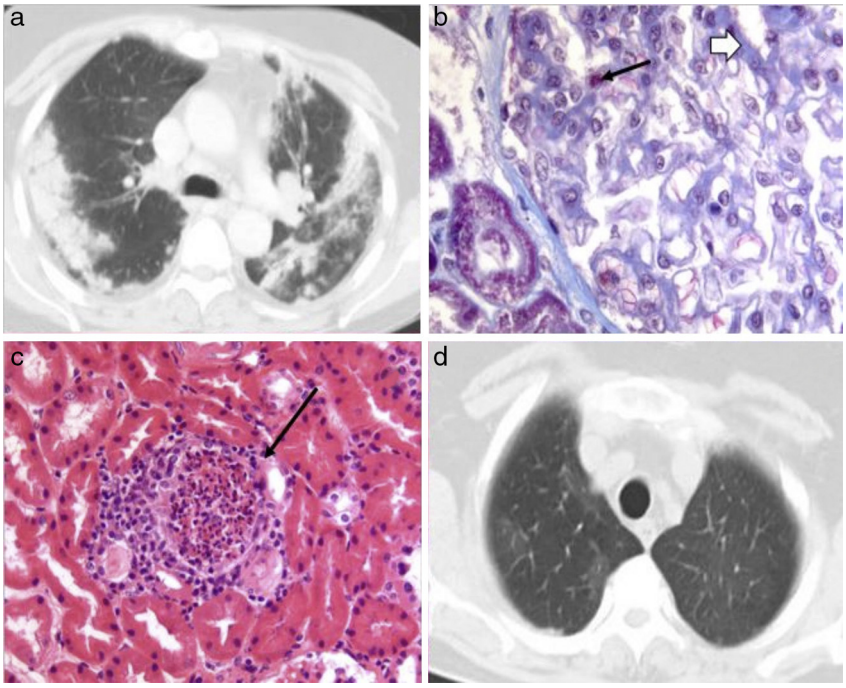

Figure 1 (Panel a) Peripheral bilateral infiltrates with air bronchogram with mediastinal lymphadenopathy. (Panel b) Mesangial proliferative glomerulonephritis with segmental involvement (white arrow) and eosinophilic inflammatory cells (black arrow). (Panel c) Tubular eosinophillic microabscess. (Panel d) Resolution after 30 days of treatment.

eosinophils have been implicated in the pathogenesis of CSS (IL-5, IL-25, eotaxin 2, eotaxin 3, etc.). Eosinophilic infiltration leads to tissue-specific damage through direct cytotoxic effects by deposition of eosinophil granule proteins and the release of reactive oxygen species or indirectly as a result of recruitment and activation of other inflammatory cells. The endothelial injury induced by the ANCA is the other physiopathological mechanism involved in the origin of this process. ANCA are present in 30–60% of the cases and most of ANCA positive-patients typically show the anti-myeloperoxidase pattern.[3] The presence, or not, of ANCA allows a distinction to be made between two subtypes of CSS. As in our patient's case, the negative-ANCA pattern is associated with a higher degree of eosinophilia (peripheral and of the tissue), parenchymal lung disease and fever. ANCA-positive patients usually show higher prevalence of necrotizing glomerulonephritis, alveolar hemorrhage, neuropathy, and other forms of vasculitic expression.[4]

Renal disease appears less frequently than in other types of vasculitis. According to published data, it is present in 20–90% of CSS cases.[5] Patients usually show a nephritic urinary sediment although there are some studies about nephrotic range proteinuria.[6] Prevailing histology points to focal necrotizing glomerulonephritis, typically seen in ANCA-positive patients. Less frequent forms include acute eosinophilic tubulointerstitial nephritis (TIN), mesangial glomerulonephritis and focal segmental glomerulosclerosis, typically seen in the ANCA-negative forms. Solans et al.[7] reported renal involvement in four out of the 32 identified patients (12.5%) diagnosed of CSS between 1977 and 1999 in Vall d'Hebrón University General Hospital in that period. Renal biopsy was taken in two patients. The histology revealed one case of focal segmental glomerulonephritis and one case of necrotizing vasculitis, respectively. Tissue-eosinophilic infiltration was not present in any kidney biopsy performed.

Besides, eosinophilic interstitial nephritis is not specific to CSS and its origin may often be attributed to a pharmacological cause or to an infectious etiology. In these cases the inflammatory infiltrates usually include neutrophils, lymphocytes, plasma cells and eosinophils. Clinical evolution tends to be favorable; however, renal stage disease at the time of diagnosis will mark the ultimate outcome. Table 1 summarizes the published cases of renal-involvement CSS with eosinophilic tubulointerstitial nephritis without other biopsy-proven renal lesions.

We think it is worth highlighting the existence of other particularities that, while not typical in CSS, were present in this case at the time of diagnosis. Asthma preceded vasculitis development in one year, a period of time shorter than usual (mean 9 years).[7] In addition, asthma severity was mild–moderate. This fact and the good control without oral steroids are associated to a good prognosis.[8] There are few CSS cases published that include lymphatic disease although it may be present in 30–40% of cases.[9] Whether such presence is a good or bad prognostic indicator this is yet to be established. Anosmia and rhinolalia are equally rare as an initial sign of sinonasal disease, usually being seen in the advanced stages of rhinosinusitis and nasal polyposis. To our knowledge, there are only two published cases of anosmia as a presenting symptom of CSS.[10,11]

Table 1 EGPA published cases presenting with eosinophilic tubulointerstitial nephritis with biopsy-proven renal lesions.

Patient no.	Author	Age/sex	sCr (mg/dL)	Hematuria	Proteinuria (g/day)	Leukocyturia (WBC/HPF)	ANCA	Histology	Eo	Vas	Therapy	Outcome (sCr; mg/dL)
1	Sinico et al.[5]	77/F	3.3	+	0.4	NA	C/PR3	TIN	+	–	PSL/AZA	2.1
2	Davenport et al.[12]	37/M	11.5	+	+++	NA	NA	TIN	+	–	PSL	5.1
Ours		62/F	0.7	++++	0.7	10–15	(–)	TIN	++	–	PSN+AZA	0.8

EGPA, eosinophilic granulomatosis with polyangiitis; WBC/HPF, white blood cells/high power field; F, female; M, male; NA, not available; sCr, serum creatinine; (–), negative; PSL, prednisolone, PNS, prednisone; AZA, azathioprine; ANCA, antineutrophil cytoplasmic antibodies; C/PR-3, proteinase-3 ANCA; TIN, tubulointerstitial nephritis; Eo, eosinophil-rich interstitial infiltrate; Vas, vasculitis.

We want to highlight the possibility of the occurrence of a polyangiitis overlap syndrome in our patient. This entity is defined as a systemic vasculitis that cannot be classified into one of the well-defined vasculitic syndromes. In our case, despite the absence of granulomas and vasculitis, the coexistence of asthma, eosinophilia, anosmia, rinolalia and eosinophilic interstitial nephritis led us to classify the case as an atypical form of CSS.

Our patient met only one of the criteria included in the last review of the Five Factor Score[13] (ear, nose or throat involvement) linked with a good outcome. However, the presence of a persistent nephritic urinary sediment as an indicator of renal disease, led us to associate AZA to the steroid treatment, after the dosage of thiopurine methyltransferase (TPMT) activity in order to prevent any potential toxicity. Several genetic polymorphisms of TPMT have been related to susceptibility to AZA-toxicity. Hepatotoxicity, mainly as abnormal liver function tests, is an uncommon side effect of AZA. Only three cases of severe cholestatic hepatitis have been reported in literature and none with CSS.[14] According to the Naranjo probability scale,[15] the prompt occurrence of a cholestatic hepatitis after the introduction of AZA, the normalization of the laboratory results after drug withdrawal and the exclusion of other causes of liver damage, strongly suggest a cholestatic hepatocellular injury caused by this drug. In our case, the TPMT*2 (A80P), TPMT*3A (A154T and Y240C), TPMT*3B (A154T) and TPMT*3C (Y240C) mutant alleles, variants associated with about 95% of cases of low or reduced enzymatic activity, were absent. However, our patient developed a severe cholestatic hepatitis which may be related to any other of the 20 variant alleles associated with reduced enzymatic activity.[13] Our case is the first reported in literature of a CSS-patient treated with AZA who developed a severe cholestatic hepatitis.

Conclusion

Churg–Strauss syndrome represents even today a true challenge for the internist. Our case is especially interesting due to the heterogenicity of its clinical expression and the infrequent form of renal involvement. It is also the first reported CSS-patient in literature who developed a severe cholestatic hepatitis following treatment with AZA. The toxicity of the available treatments forces us to closely monitor these patients to avoid excess morbidity added to the pathology itself.

Conflict of interest

The authors declare having no conflict of interest.

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