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Occam's razor reveals a hidden Churg-Strauss syndrome

Case Report

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Abstract: A 28 year-old caucasian lady, with nine years of uncontrolled bronchial asthma, rhinosinusitis and mild upper limb paresthesia, came to our attention to be followed for coeliac disease (CD). She had a biopsy performed elsewhere which proved the diagnosis five years before. Since there was no clinical improvement on a strict gluten-free diet, we re-evaluated the slides of her duodenal biopsies and we found an overestimation of the duodenal lesions due to the wrong orientation of the specimens. Moreover, she had never had positive CD-related antibodies and she was negative for DQ2/DQ8 MHC Class II heterodimers. Months later, she referred she was suffering from diffuse joint pain, epistaxis and a substantial weight loss. A few days later she was hospitalized because of a sudden onset of dyspnea, peripheral edema and pleural effusion. Her echocardiogram showed global left ventricular hypokenesia with an ejection fraction of 24%. The patient was discharged with a diagnosis of dilated cardiomyopathy and NYHA Class II. After a large spectrum of haematological exams, the diagnosis of Churg Strauss Syndrome (CSS), a rare multisystemic small-vessel necrotizing vasculitis, was confirmed by the presence of four/five out of six diagnostic American College of Rheumatology classification criteria (Asthma, Eosinophilia >10%, Neuropathy, Non-fixed pulmonary infiltrates, Paranasal sinus abnormality and Biopsy containing a blood vessel with extravascular eosinophils). Our patient had been under-diagnosed by pulmonologist and by gastroenterologists although she presented the criteria required for CSS diagnosis. Our case report emphasizes that often seemingly unrelated symptoms can be caused by a single rare clinical complex.

Keywords: *Coeliac Disease • Churg-Strauss Syndrome • Eosinophils • Asthma*

1. Introduction

In daily clinical practice too often the presence of systemic diseases forces the clinician to involve several other specialists. As result, the many points of view expressed take the doctor away from reaching a definitive and unequivocal diagnosis.

Churg–Strauss syndrome (CSS) is a rare systemic small-vessel necrotizing vasculitis. Its main clinical characteristics, some potentially life-threatening, are now well known, as are its usual successive phases, from allergic rhinitis to asthma, and finally vasculitis. Conversely, physiopathogenetic mechanisms are not completely elucidated and clearly multiply, thereby suggesting the existence of different disease subtypes.

CSS has an annual incidence ranging between 0.5 and 6.8 per million inhabitants [1] and a prevalence of 10.7–14 per million inhabitants [2]. In addition to its most frequent and well known characteristic manifestations, especially allergic rhinitis, sinus polyposis and late-onset asthma [3], several patient subgroups might possibly be distinguished clinically or diagnosed based on biological parameters, like antineutrophil cytoplasm autoantibody (ANCA) status [4]. It was demonstrated that therapeutic strategies can be adjusted according to the presence or absence of some clinical parameters carrying a poorer prognosis, but it is not known whether outcomes of these more recently identified patient subgroups also differ.

Our case report describes how often a single sys-

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temic disease may explain many seemingly unrelated clinical manifestations and how a critical patient can have the benefit of a timely diagnosis.

2. Case report

A 28 year-old caucasian lady, with nine years of uncontrolled bronchial asthma, rhinosinusitis with nasal polyps and mild upper limb paresthesia, came to our Operative Unit to be followed for coeliac disease (CD). She had a biopsy performed elsewhere which proved diagnosis five years before.

She appeared pale and thin (weight: 53 kg, height: 1.63 m, BMI: 20) but, despite the presence of an important wheezing, she was in good general condition. Routine analyses were normal, except for the presence of iron deficiency anemia (hemoglobin: 11.4 g/dl; ferritin: 5 ng/ml). Since there was no clinical improvement on a strict gluten-free diet, we decided to re-evaluate the diagnosis of CD, by referring the slides of duodenal biopsies to a skilled pathologist, who found an overestimation of the duodenal lesions due to the wrong orientation of the specimens (Figure 1). Moreover, she had never had positive CD-related antibodies and she was negative for DQ2/DQ8 MHC Class II heterodimers [5].

Months later, she came back referring she was suffering from joint pain, located mainly in the sternum, wrist and elbows, epistaxis and also subungual hemorrhage. She reported a purpuric and ecchymatic rash with nodules of up to 10 cm in diameter on her abdomen and a substantial weight loss (10 kg in one month). She had rheumatologic blood tests performed, but a few days later she was hospitalized because of a sudden onset of dyspnea, peripheral edema, ascites and pleural effusion.

On admission, her echocardiogram showed global left ventricular hypokenesia with an ejection fraction of 24%. The patient was discharged with a diagnosis of dilated cardiomyopathy and NYHA Class II.

Endomyocardial biopsy showed interstitial and endocardial fibrosis together with myocyte hypertrophy, without inflammatory infiltrates, thus suggesting a non-specific cardiomyopathy.

Meanwhile, the responses of rheumatological tests showed: presence of ANA (1:80, homogeneous pattern), RA-test: 117 Ul/mL (<40 Ul/ml), C3: 195 mg/dl (55-120 mg/dl), MPO-ANCA, PR3-ANCA (ELISA) and P-ANCA and C-ANCA (IF) were negative. Moreover, a high concentration of eosinophils (10500/microL, 53.5% of total WBC), CRP 15016 (100-6000), VES 99 mm/h (<35 mm/h) and fibrinogen 5 g/L (2-4 g/L) was found in the peripheral blood. The stool samples for parasites and ova were negative.

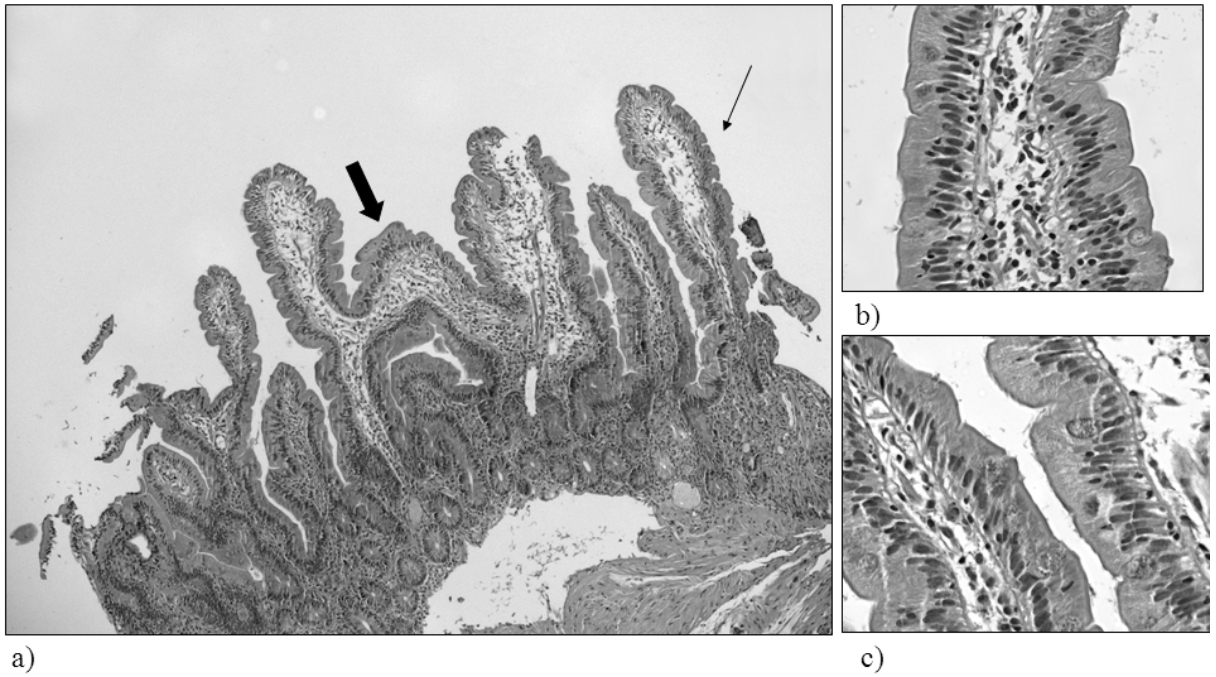

Figure 1. a) Histological picture of duodenal mucosa showing normal villous architecture (thin arrow), and the pitfall "atrophy-like" picture due to poorly oriented specimen (thick arrow) (Hematoxilin-eosin, original magnification 100x);
b) and c) histological picture of duodenal mucosa showing normal villi with normal intraepithelial lymphocytes (IEL) count (less than 40 IEL/100 enterocytes) (Hematoxilin-eosin, original magnification 200x).

The high concentration of eosinophils suggested the possibility of a differential diagnosis mainly between two rare conditions: Hypereosinophilic Syndrome (HES) and Churg-Strauss Syndrome. HES, but also lymphocytic or myeloproliferative HES, chronic eosinophilic leukemia and other myeloid neoplasms with eosinophilia are among the several differential diagnoses of CSS [6]. Indeed, CSS can clinically closely resemble these entities, differing mainly by the presence of systemic vasculitis [7]. The presence of a prodromal asthmatic phase of nine years indicated a more likely hypothesis of CSS.

The diagnosis of CSS was then confirmed by the presence of four/five out of six diagnostic American College of Rheumatology classification criteria (Asthma, Eosinophilia >10%, Neuropathy, Non-fixed pulmonary infiltrates, Paranasal sinus abnormality and Biopsy containing a blood vessel with extravascular eosinophils) [8]. The last criterion could possibly be found in the bowel involvement which mistakenly led to the diagnosis of CD, or in the heart damage which could be secondary to vasculitis because of the marked myocardial fibrosis. Unfortunately, intestinal biopsies did not reach blood vessels and the myocardial biopsy was probably performed too late. The multifocal appearance and the regression of symptoms could probably be due to the steroids taken by the patient for asthma.

The woman showed elevated values of CRP and fibrinogen, but was ANCA-negative, a frequent finding in patients with a more systemic manifestation of vasculitis, and typical of CSS patients with cardiac involvement [3].

3. Discussion

Although the diagnosis of CSS is often difficult, our case could be considered a paradigmatic one overshadowed by other wrong diagnoses.

The presence of uncontrolled asthma was underestimated and all the specialists involved (gastroenterologist, pulmonologist and cardiologist) looked only at their field of study.

Unlike the CSS, CD is a widespread disease in the general population and too often called into question in complex clinical pictures. Gastrointestinal manifestations of CSS are quite common (37-62% of all cases) [9] and gastroenterologists should be familiar with the clinical appearance of CSS. In some cases, eosinophilic gastroenteritis may be the prodrome of CSS. Common gastrointestinal symptoms included abdominal pain, bloody stools, diarrhea, occasional vomiting and multiple ulcers may be seen and may lead to perforation.

The small intestine is the most common site of involvement and is most commonly perforated, but a case report of multiple colonic ulcers and perforation exists [10].

This kind of clinical manifestations may be confounding in the differential diagnosis with CD, because of the similar expression of the disease.

A simple distinction between CSS patients is based on their ANCA status. Approximately only 40% of CSS patients are ANCA-positive [4], mainly with a perinuclear immunofluorescence-labeling pattern (P-ANCA) and antimyeloperoxidase (anti-MPO) specificity in an enzyme-linked immunosorbent assay.

Currently, several research teams are attempting to identify reliable marker(s) of CSS activity, like serum eosinophil cationic protein [11], IL-5 [12], or eotaxin-3 (CCL26), an eosinotactic chemokine mainly expressed on vascular endothelial cells and dermal fibroblasts, after IL-4 and IL-13 stimulation, and in bronchial tissue during an allergen challenge [13].

This demonstrates that many efforts must still be done in order to understand pathogenesis of CSS and to facilitate its diagnostic process.

4. Conclusions

Our patient was under-diagnosed by a pneumologist and by gastroenterologists although she manifested the criteria required for CSS diagnosis. Early diagnosis and treatment of CSS are mandatory, in order to avoid life-threatening complications, improve the quality of life and prolong the survival of patients.

It has been shown that patients at CSS onset can initially be treated with corticosteroids alone [14], because it achieves remission in more than 90% of them. However, the relapse rate reaches 35% after a mean follow-up of 56 months, mainly during the first year of treatment, and more than 75% of the patients cannot be weaned off corticosteroids, chiefly because of residual asthma [14] and, thus, some of them ultimately require the adjunction of an immunosuppressant to control CSS.

Our patient, after the diagnosis, started steroid therapy (prednisone 5 mg/die) and, after a one year follow-up on a free diet, she is in good general condition. Heart function is now well controlled (left ventricular ejection fraction: 42%), the pulmonary function is stable and she has not had any recurrence of symptoms involving CSS. A careful follow-up program will allow us to prevent possible relapses.

This case could represent an update of Occam's statement: "Pluralitas non est ponenda sine necessitate". In fact, the chance of multiple disabling diagnoses is unlikely in a previously healthy young woman, while a single rheumatic disease, embracing various organs, is more probable.

References

[1] Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract Res Clin Rheumatol 2005; 19:191-207

[2] Mohammad AJ, Jacobsson LT, Mahr AD, et al. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg–Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford) 2007; 46:1329-1337

[3] Pagnoux C, Guilpain P, Guillevin L. Churg–Strauss syndrome. Curr Opin Rheumatol 2007; 19:25-32

[4] Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg–Strauss syndrome. Arthritis Rheum 2005; 52:2926-2935

[5] Megiorni F, Mora B, Bonamico M,et al. HLA-DQ and risk gradient for celiac disease. Hum Immunol. 2009;70:55-9

[6] Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. J Allergy Clin Immunol 2006; 117:1292-1302

[7] Hellmich B, Holl-Ulrich K, Merz H, Gross WL. Hypereosinophilic syndrome and Churg–Strauss syndrome: is it clinically relevant to differentiate these syndromes? [in German]. Internist (Berl) 2008; 49:286-296

[8] Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss Syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100

[9] Singh R, Singh D, Abdou N. Churg-Strauss syndrome presenting as acute abdomen: are gastrointestinal manifestations an indicator of poor prognosis? Int J Rheum Dis 2009;12:161-5

[10] Cojocaru M, Cojocaru IM, Silosi I et al. Gastrointestinal manifestations in systemic autoimmune diseases. Maedica. 2011;6:45-51

[11] Guilpain P, Auclair JF, Tamby MC, et al. Serum eosinophil cationic protein: a marker of disease activity in Churg–Strauss syndrome. Ann N Y Acad Sci 2007; 1107:392-399

[12] Tsukadaira A, Okubo Y, Kitano K, et al. Eosinophil active cytokines and surface analysis of eosinophils in Churg–Strauss syndrome. Allergy Asthma Proc 1999; 20:39-44

[13] Polzer K, Karonitsch T, Neumann T, et al. Eotaxin-3 is involved in Churg–Strauss syndrome: a serum marker closely correlating with disease activity. Rheumatology (Oxford) 2008; 47:804-808

[14] Ribi C, Cohen P, Pagnoux C, et al. Treatment of Churg–Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis Rheum 2008; 58:586-594