Churg–Strauss Syndrome with Eosinophilic Myocarditis

A Clinical Pathology Conference Held by the Division of Rheumatology at Hospital for Special Surgery

Alana B. Levine, MD · George Kalliolias, PhD · Mark Heaney, MD, PhD · Yoshimi Endo, MD · Adam Gersten, MD · Jonathan W. Weinsaft, MD · Robert F. Spiera, MD · Anne Bass, MD · Doruk Erkan, MD

Received: 30 June 2011/Accepted: 9 April 2012/Published online: 23 June 2012
© Hospital for Special Surgery 2012

Keywords Churg–Strauss Syndrome · eosinophilic myocarditis · hypereosinophilia

History and Physical Examination

An 85-year-old Chinese woman with a 4-year history of asthma presented with a severe headache for 1 week and substernal chest pain for 1 day.

Seven days prior to presentation, the patient was seen by her primary care physician for evaluation of a new-onset severe headache; she was prescribed an unknown dose of ibuprofen, which she took for 2 days before developing facial swelling and hives. The facial swelling and rash resolved

shortly after discontinuing ibuprofen, but the headache continued. Two days prior to presentation, the patient went to the emergency room because of her headache; a non-contrast head computed tomography (CT) scan was negative and she was discharged without further workup. Two days later, the patient developed substernal chest pain. She returned to the emergency room and was admitted for further evaluation.

On admission, the patient reported frontal and temporal headache without nausea or photosensitivity. She also complained of gradually intensifying, substernal, nonpleuritic chest pain that did not radiate and was not associated with cough or shortness of breath. She denied fever, chills, changes in weight, rash, alopecia, visual disturbance, oral or nasal ulcers, sinus pain, hemoptysis, abdominal pain, nausea, vomiting, diarrhea, dysuria, hematuria, joint pain, or focal weakness. She reported intermittent episodes of dry cough and shortness of breath over the past 4 years that had been diagnosed and treated as asthma.

Past medical history was significant for pulmonary tuberculosis, diagnosed and treated with an unknown medication regimen in 1968. Despite this treatment, she developed disseminated tuberculosis of the thoracic and pelvic lymph nodes, liver, and spine in 1990. She required spine surgery at that time and was treated with an unknown multidrug regimen for the next 4 years. Her other medical history included asthma, hyperlipidemia, and gastroesophageal reflux disease. She had undergone a meningioma resection in the late 1980s.

Medications on admission included metoprolol 50 mg daily, aspirin 81 mg daily, simvastatin 20 mg daily, fluticasone/salmeterol 250 mcg inhaled twice daily, gabapentin 300 mg three times daily, pantoprazole 20 mg daily, trazadone 25 mg nightly, and zolpidem 5 mg nightly. There were no known drug allergies.

The patient was born in China and moved to the USA in 1968. She had last traveled back to China in 1990. She lived alone but had family nearby. She did not use tobacco, alcohol, or illicit drugs. She had no family history of autoimmune disease.

A. B. Levine, MD (✉) · G. Kalliolias, PhD · R. F. Spiera, MD ·
A. Bass, MD · D. Erkan, MD
Division of Rheumatology, Hospital for Special Surgery,
535 East 70th Street,
New York, NY 10021, USA
e-mail: levinea@hss.edu

M. Heaney, MD, PhD
Department of Medicine, Memorial Sloan-Kettering Cancer Center,
New York, NY 10065, USA

Y. Endo, MD
Department of Radiology, Hospital for Special Surgery,
535 East 70th Street,
New York, NY 10021, USA

A. Gersten, MD
Department of Pathology,
Weill-Cornell Medical College–New York Presbyterian Hospital,
New York, NY 10065, USA

J. W. Weinsaft, MD
Division of Cardiology,
Weill-Cornell Medical College–New York Presbyterian Hospital,
New York, NY 10065, USA

On physical examination at the time of admission, the patient appeared well-nourished. She was afebrile and normotensive. Her general physical examination was otherwise significant for an apical systolic murmur and bibasilar crackles. Her distal pulses were intact. There were no carotid or abdominal bruits. She had no arthritis or rashes. The neurological exam was unremarkable.

Laboratory evaluation at the time of admission revealed a leukocytosis with prominent eosinophilia (Table 1). Chest radiograph and chest CT showed no acute disease (see radiology discussion below).

While on telemetry monitoring on hospital day 3, the patient's troponin trended upward, peaking at 26.66 ng/mL. Her electrocardiogram showed new ST depressions in the anterior leads. The patient underwent cardiac catheterization on hospital day 4 which showed nonobstructive coronary artery disease. Cardiac magnetic resonance imaging (MRI) was performed (see radiology discussion below).

On hospital day 5, the patient complained of the new onset of wrist pain and weakness. A brain MRI, right ventricular myocardial biopsy, and bone marrow biopsy were performed (see radiology and pathology discussions below). Rheumatology consultation was requested to rule out systemic vasculitis. On physical examination the patient was noted to have bilateral metacarpophalangeal (MCP) and wrist tenderness with mild swelling. She had bilateral wrist drop as well as splinter hemorrhages of the fingernails. Serologic studies were ordered (Table 1).

Radiology Discussion—Imaging Interpretation

Chest Imaging

Chest radiography and a chest CT scan showed evidence of old granulomatous disease with mild emphysematous changes.

Cardiac Imaging

Echocardiography demonstrated normal left ventricular size and systolic function (ejection fraction 57 %) without regional wall motion abnormalities. Pulmonary arterial pressure was moderately elevated (PA systolic=46 mmHg). Valvular function was significant for moderate mitral, mild–moderate aortic, and mild–moderate tricuspid regurgitation.

Cardiovascular MRI was performed for further assessment of cardiac geometry, function, and tissue characteristics (Fig. 1). Functional (cine) MRI confirmed normal left ventricular size and function. Tissue characterization via delayed enhancement (DE-) MRI demonstrated myocardial scar/infarction involving the subendocardial aspect of the mid-distal anterior wall and septum. While the pattern of myocardial scar appeared in a typical coronary vascular (i.e., left anterior descending arterial) distribution, an atypical pattern of myocarditis could not be fully excluded.

Central Nervous System Imaging

Non-contrast CT scan of the brain performed at the time of the patient's emergency room visit 2 days prior to admission

Table 1 Laboratory values

Value	Admission	Hospital day 5	Reference range
White blood cell	16.3	22.1	3.4–11.2 K/uL
Differential			
Neutrophils	38	35	45–75 %
Lymphocytes	7	4	20–50 %
Monocytes	3	3	2–11 %
Eosinophils	52	58	0–5 %
Basophils	0	0	0–1 %
Hemoglobin	11.9	10.5	11.7–16.0 g/dL
Platelets	180	141	150–450 K/uL
Sodium	138	137	136–144 mmol/L
Potassium	4.1	3.8	3.2–5.2 mmol/L
Chloride	107	105	101–111 mmol/L
Carbon dioxide	27	26	22–32 mmol/L
Blood urea nitrogen	7	21	8–20 mg/dL
Creatinine	0.5	0.7	0.4–1.0 mg/dL
Glucose	112	90	74–118 mg/dL
Total protein	5.3	5.8	6.1–7.9 g/dL
Albumin	2.4	2.1	3.5–4.8 g/dL
Aspartate aminotransferase	27	45	15–41 U/L
Alanine aminotransferase	21	25	14–54 U/L
Total bilirubin	0.8	0.7	0.3–1.2 mg/dL
Alkaline phosphatase	54	54	32–91 U/L
International normalized ratio	1.0	1.0	0.9–1.1
Protime	10.8	10.1	9.4–11.5 s
Partial thromboplastin time	32.8	33.8	25.0–35.0 s
Urinalysis	Negative	Negative	Negative
Creatine kinase	113	574	38–234 U/L
Troponin	0.13	26.66	0.01–0.04 ng/mL
B-type natriuretic peptide	134	1,711	<100 pg/mL
Estimated sedimentation rate	34	74	0–30 mm/h
High-sensitivity C-reactive protein	—	72.87	< 1.00 mg/L
Anti-nuclear antibody	—	Negative	Negative
Myeloperoxidase antibody	—	0	0–19 AU/mL
Proteinase 3 antibody	—	1	0–19 AU/mL
Rheumatoid factor	—	46.4	0–20.0 IU/mL
Angiotensin-converting enzyme	—	37	9–67 U/L
Complement 3	—	103.0	85.0–193.0 mg/dL
Complement 4	—	31.7	12.0–36.0 mg/dL
IgG	—	1,880	639–1,349 mg/dL
IgM	—	47	56–352 mg/dL
IgA	—	288	70–312 mg/dL
IgE	—	3,785.2	1.3–165.3 IU/mL
Echinococcus IgG	—	0.1	0.0–0.9 IV
Coccidioides antibody	—	Negative	Negative
Schistosoma IgG	—	0	0.0–0.1 OD
Strongiloides IgG	—	0.42	<1.49 IV
Trichinella antibody	—	Negative	Negative
HIV	Negative	—	Negative
Blood cultures	No growth	No growth	No growth

Abnormal values in bold

demonstrated evidence of prior right frontotemporal craniotomy and encephalomalacia of the adjacent frontal lobe, consistent with the history of remote meningioma resection.

Fig. 1. Representative cardiac magnetic resonance (CMR) images as acquired using a post-contrast inversion recovery pulse sequence. Images are displayed in short-axis orientation (mid-distal left ventricle). Note that

CMR demonstrated prominent subendocardial hyperenhancement (*white arrows*) involving the mid-distal septum, consistent with preferential subendocardial involvement in the context of eosinophilic infiltration

There was no hemorrhage or acute intracranial abnormality. Subsequent MRI of the brain performed on day 5 of admission demonstrated multiple foci of restricted diffusion in the distribution of both anterior and posterior circulations consistent with acute to subacute infarcts involving bilateral cerebral hemispheres, cerebellum, and deep gray and white matter (including the basal ganglia and corpus callosum; Fig. 2a, b). There was mild generalized parenchymal volume loss and evidence of chronic microvascular ischemic disease without hemorrhage. Magnetic resonance angiogram (MRA) without contrast demonstrated patent intracranial vessels of the anterior and posterior circulations as well as the vertebral and carotid arteries of the neck (Fig. 3).

Clinical Discussion (Differential Diagnosis)

Based on the history, physical examination, laboratory studies, and imaging studies, the differential diagnosis included Churg–Strauss syndrome (CSS), hypereosinophilic syndrome (HES), neoplastic disease (including Hodgkin's and non-Hodgkin's lymphomas, adenocarcinoma, and myeloproliferative neoplasms such as chronic eosinophilic leukemia [CEL] and mastocytosis), rheumatoid arthritis with vasculitis, systemic lupus erythematosus, other small- to medium-vessel vasculitis (cryoglobulinemia, granulomatosis with polyangiitis [Wegener's], microscopic polyangiitis), sarcoidosis, infection, or a drug reaction.

Pathology Discussion—Histologic Interpretation

Right Ventricular Biopsy

The specimen consisted of five fragments of tissue from the right ventricle, the largest of which measured 3 mm. At low power, myocytes and an interstitial infiltrate were seen. The specimen contained very little endocardium and no large blood vessels. At higher power, the interstitial infiltrate consisted primarily of eosinophils with some lymphocytes and neutrophils (Fig. 4). Some fragments demonstrated basophilic areas of myocardial necrosis and concretions of eosinophilic granules known as Charcot–Leyden crystals. The pathologic impression was of an active myocarditis with a prominent eosinophilic infiltrate and myocardial necrosis. Vasculitis was not specifically identified in the sample.

Bone Marrow Biopsy

At low power, cartilage, soft tissue, bone, and slightly hypercellular marrow (typical for the patient's age) were seen. At higher power, megakaryocytes, many eosinophils, and maturing cells were seen (Fig. 5). There were no blasts. Cytogenetics were negative for PDGFR α or PDGFR β rearrangements, which significantly decreased the likelihood of an underlying hematological malignancy (see hematology discussion below). The pathologic impression was of a reactive and hyper-eosinophilic bone marrow.

Fig. 2. a and b: Two axial diffusion-weighted MRI sequences demonstrating bilateral foci of restricted diffusion compatible with infarcts (*arrows*) in the distribution of both the anterior and posterior circulations

Fig. 3. Maximum intensity projection image from a 3-D time-of-flight MR angiogram of the brain demonstrating normal intracranial arteries without stenoses or occlusions

Diagnosis

Churg–Strauss Syndrome

Clinical Discussion (Hematology)

This is a case of an 85-year-old woman with a history of asthma presenting with headaches, non-ST elevation myocardial infarction (NSTEMI), bilateral wrist and MCP arthritis, mononeuritis multiplex, multiple infarctions on MRI, leukocytosis with a profound eosinophilia, and eosinophilic infiltration of the myocardium. The presence of striking peripheral eosinophilia, the eosinophilic infiltration of myocardium, and mononeuritis multiplex were the features most suggestive of CSS (further discussed below—Rheumatology section).

Other eosinophilic conditions that were considered in this patient include idiopathic hypereosinophilic syndrome and chronic eosinophilic leukemia. Idiopathic HES is defined as sustained peripheral eosinophilia with an absolute eosinophil count of more than $1,500 \mu\text{L}^{-1}$ and is a diagnosis of exclusion.

Chronic eosinophilic leukemia is a rare clonal chronic myeloproliferative disorder characterized by overproduction of morphologically normal eosinophils in bone marrow with peripheral eosinophilia and solid organ infiltration.

The clinical course of idiopathic HES is quite variable and relates to the sites of eosinophilic infiltration. Severity of disease does not necessarily correlate with the degree of peripheral eosinophilia. Rash is one of the most common clinical signs in HES and many patients also develop gastrointestinal symptoms. Fibrosis may occur in the heart, lungs, and bone marrow. Patients with CEL typically have involvement of the spleen and less commonly of the skin, central nervous system, heart, and liver; the muscles, lung, and nasal sinus may also be affected. Chronic eosinophilic leukemia is characteristically amenable to treatment with imatinib, which can induce hematologic and molecular remission [5, 18].

In 2008, the revised WHO classification criteria for myeloproliferative neoplasms reorganized HES and CEL based on molecular information. According to the new classification system, “myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFR α , PDGFR β , and PIP1L1” are now assigned to their own category [28]. The diagnoses of idiopathic HES and CEL are supported by molecular genetic testing of the peripheral blood using (1) fluorescence in situ hybridization to test for the CHIC2 locus and/or (2) reverse transcriptase polymerase chain reaction to detect the FIP1L1-PDGFR α mutation [7]. If peripheral blood testing is negative, bone marrow evaluation should be pursued as testing for PDGFR α rearrangement in the bone marrow is more sensitive than in the peripheral blood. In the present case, the slightly hypercellular bone marrow was nonspecific due to the patient’s age. The negative cytogenetic testing for PDGFR α or PDGFR β rearrangements made a diagnosis of idiopathic HES or CEL very unlikely.

Fig. 4. The myocardium contains an interstitial infiltrate consisting of primarily eosinophils along with lymphocytes and neutrophils ($\times 40$, H&E)

Fig. 5. The bone marrow is hypercellular with markedly increased eosinophils ($\times 40$, H&E)

Clinical Discussion (Rheumatology)

Churg–Strauss syndrome is a systemic, necrotizing small- to medium-vessel vasculitis that is typically characterized by asthma, hypereosinophilia, and extrapulmonary vasculitis [13]. It is classified as an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, although ANCA is detected in only about 40 % of CSS cases [23]. When present, ANCA is usually in a perinuclear pattern by immunofluorescence testing, and enzyme-linked immunosorbent assay testing reveals antibody specificity for myeloperoxidase. Anti-neutrophil cytoplasmic antibody positivity in CSS is associated with renal disease, pulmonary hemorrhage, mononeuritis multiplex, and worse outcomes [26].

The diagnosis of CSS is generally made clinically and may require observation of the patient over time. The American College of Rheumatology (ACR) criteria required for the diagnosis of CSS are listed in Table 2; this patient has three of the six criteria, including asthma, peripheral eosinophilia, and mononeuritis multiplex [17]. Lanham et al. described three phases of the disease which may occur sequentially or simultaneously—a prodromal phase, an eosinophilic phase, and a vasculitic phase [16]. In the prodromal phase of the disease, most patients have asthma, atopic disease, or other allergic symptoms that may be misdiagnosed and treated as recurrent pneumonia or bacterial infections. The eosinophilic stage is manifested by peripheral eosinophilia, eosinophilic pulmonary disease, and/or eosinophilic gastroenteritis. In the vasculitic phase patients have constitutional and systemic vasculitic manifestations that may be related to vascular and extravascular granulomatosis. This patient had characteristics of both the eosinophilic and vasculitic phases of disease.

One of the strongest clinical factors favoring a diagnosis of CSS in this case is the involvement of the peripheral nervous system with bilateral wrist drop, or mononeuritis multiplex. The patient also complained of MCP and wrist tenderness with appreciable synovitis. These findings would be uncommon in HES or CEL. Laboratory studies showed leukocytosis with eosinophilia which would be typical of CSS. While the mean age of onset of CSS is 55 years, placing this 85-year-old patient at the older end of the spectrum for diagnosis, the rarity of this disease makes it difficult to rule out this diagnosis on the basis of the patient's age.

Table 2 American College of Rheumatology (ACR) 1990 Criteria for the Classification of Churg–Strauss Syndrome. Adapted from 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. with permission from John Wiley and Sons

Asthma
Peripheral blood eosinophilia greater than 10 % on differential leukocyte count
Mononeuropathy (including multiplex) or polyneuropathy
Non-fixed pulmonary infiltrates on chest radiography
Paranasal sinus abnormality
Biopsy containing a blood vessel with extravascular eosinophils

The presence of ≥ 4 criteria has a sensitivity of 85 % and a specificity of 99.7 % for the diagnosis of CSS

Cardiac involvement is common in CSS, with myocardial abnormalities found in more than 50 % of autopsies in Churg and Strauss' original cohort [4]. Cardiac manifestations may include acute and/or constrictive pericarditis, restrictive or dilated cardiomyopathy, myocarditis, intracavitary thrombi, arrhythmias, and sudden death. When present, these abnormalities result in approximately 50 % of deaths in CSS [20]. Cardiac MRI has been used to detect intracavitary thrombi as well as focal areas of delayed enhancement which suggest inflammation (due to eosinophilic infiltration), ischemia, and/or fibrosis [1]. In the present case, the delayed enhancement seen on cardiac MRI corresponded to inflammation resulting from eosinophilic infiltration and myocardial ischemia as evidenced by NSTEMI.

Cerebral infarction is an uncommon manifestation of CSS, occurring in less than 10 % of patients in one series [25], and is thought to result from vasculitis. When vasculitis presents as infarcts, MRI usually shows multiple, bilateral lesions involving both gray and white matter [8], as seen in the present case. Despite a normal MRA of the intracranial arteries, cerebral vasculitis should still be considered; partly related to the inferior spatial resolution, MRA is considered to be less accurate than conventional angiogram for detection of vasculitis, particularly for the smaller, peripheral arterial branches [11, 27]. Of note, even conventional angiogram can have false-negative results.

The Five-Factors Score (FFS) is used to evaluate prognosis at the time of diagnosis of the systemic necrotizing vasculidities and also can be used to guide management decisions (Table 3) [10]. This score, originally devised by Guillevin et al., considers cardiac, gastrointestinal, renal (creatinine and proteinuria), and CNS involvement in vasculitic syndromes. Five-year mortality is 12 % for patients with a score of 0, 26 % for those with a score of 1, and 46 % for those with a score ≥ 2 . Our patient had a FFS of 2, indicating a poor prognosis.

Corticosteroids are the mainstay of treatment for CSS. Limited disease (involving only the sinuses and skin, for example) can be managed with steroids alone, typically prednisone 1 mg/kg per day or its equivalent [21]. In more advanced disease (such as patients with cardiac or neurological involvement), pulse steroids and cyclophosphamide, generally given intravenously, are used for induction of remission [9]. Methotrexate, azathioprine, and cyclosporine have been used for maintenance of remission. Currently,

Table 3 Five-Factors Score^a in Churg–Strauss Syndrome. Adapted with permission from Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75:17–28

Cardiac involvement
Gastrointestinal disease (bleeding, perforation, infarction, or pancreatitis)
Renal insufficiency (plasma creatinine concentration >1.6 mg/dL [141 mmol/L])
Proteinuria (>1 g/day)
Central nervous system involvement

^a One point assigned to each factor

there are no randomized, placebo-controlled trials or head-to-head comparisons of medications specifically for patients with CSS. The successful use of rituximab for the treatment of refractory CSS has been described in case reports [6, 24] as well as in a recent open-label pilot study of three CSS patients with associated renal disease [3].

Immunology Discussion

Normally, eosinophils represent only 0–7 % of peripheral leukocytes and under physiologic conditions they populate the gastrointestinal tract, thymus, uterus, and mammary glands [2]. In the thymus, eosinophils function as antigen-presenting cells and participate in negative selection. In the uterus, they facilitate blastocyst implantation and might protect against infections. In mammary glands, eosinophils may drive duct development by producing transforming growth factor beta (TGF- β). Eosinophils also participate in the defense against several types of pathogens including helminthes, bacteria, viruses, and fungi [12]. Despite their physiologic roles, high numbers of eosinophils in the peripheral blood and within tissue infiltrates is the hallmark of CSS and hypereosinophilic syndrome [29].

Eosinophils are generated in the bone marrow from hematopoietic progenitors under the influence of growth factors and cytokines (including granulocyte macrophage colony-stimulating factor, interleukin (IL)-3, and IL-5); subsequently IL-5 mobilizes eosinophils to the bloodstream. There, adhesion molecules, chemokines (CCL26/eotaxin-3) and chemokine receptors (CCR3), induced by Th2 cytokines (IL-4 and IL-13), regulate the trafficking of eosinophils to peripheral tissues [2, 12]. Recently, it has been suggested that eosinophilia in CSS results from the functions of Th2 cytokines (IL-4, IL-5, and IL-13) and eotaxin-3 [29]. Churg–Strauss syndrome often develops in a Th2 background (mainly in the context of asthma) and elevated IL-5 has been found in the serum and bronchoalveolar lavage of patients with CSS. In addition, eotaxin-3 is expressed in affected tissues and is high in the serum of CSS patients. Moreover, T-cells derived from CSS patients produce *ex vivo* high IL-4 and IL-13 [29].

The main obstacles for studying the pathogenesis of CSS are the rarity of the disease and the lack of appropriate animal models. A critical question for CSS pathogenesis is whether eosinophils are effector cells or simply innocent bystanders. Eosinophils have an inflammatory and tissue destructive potential. They bear granules containing a number of cytotoxic mediators, including major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase, and eosinophil-derived neurotoxin. Eosinophils also produce a variety of pro-inflammatory cytokines, chemokines, and lipid mediators (including platelet-activating factor and leukotrienes) [2, 12]. The presence of high serum ECP and tissue expression of MBP in patients with CSS suggest that eosinophils may have a pathogenic role in these patients. In addition, after treatment with steroids, patients with CSS demonstrate a parallel decrease in peripheral eosinophilia. In this context, targeting eosinophils may represent an attractive treatment strategy at least for a subset of CSS patients [29].

Conventional therapies used to treat CSS, specifically steroids, rapidly decrease the number of eosinophils, but are nonspecific and have concerning side effects profiles. Therapies that specifically target eosinophils have been developed recently based on the advances in knowledge of eosinophil generation, mobilization, and trafficking. Different strategies to target IL-5 include a monoclonal antibody that binds and neutralizes IL-5 (mepolizumab and reslizumab), or a monoclonal antibody that targets the specific alpha subunit of IL-5 receptor (MEDI-563) that prevents the binding of IL-5 and depletes eosinophils by fixing complement [12]. These molecules, and especially mepolizumab, have been used in asthma, hypereosinophilic syndrome, and CSS [14, 15, 19, 22]. Two small studies in CSS show that mepolizumab can provide both clinical benefit and an important steroid-sparing effect [14, 15]. Finally, monoclonal antibodies targeting adhesion molecules, IL-13, eotaxins, and a small molecule that targets CCR3 are under investigation [12].

Patient Follow-up

On hospital day 9, the patient began treatment with methylprednisolone 1,000 mg daily given intravenously for 3 days for a presumptive diagnosis of CSS; peripheral leukocyte and eosinophil counts dropped precipitously following the first dose. She was maintained on prednisone 40 mg daily thereafter with mild improvement in synovitis but no improvement in wrist extension. Rituximab was considered as a steroid-sparing agent given the potential risks of cyclophosphamide administration in this patient with a history of disseminated tuberculosis. On hospital day 12, the patient was found to be in atrial fibrillation and required cardioversion. On hospital day 13, the patient suffered a cardiac arrest and died. Her family declined autopsy.

Conclusions

This case exemplifies the diagnostic challenges faced when evaluating patients with hypereosinophilia. It also demonstrates the potential severity and fatal consequences of cardiac involvement in CSS. The patient's complex infectious history complicated the decision to initiate disease-modifying treatment. Randomized clinical trials and studies of investigational treatments are warranted to improve outcomes in CSS patients.

Disclosures RS receives consulting and research funding from Roche-Genentech. All other author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution has approved the reporting of the case, that all investigations were conducted in conformity with the ethical principles of research, and that informed consent for participating in the study was obtained.

References

1. Bhagirath KM, Paulson K, Ahmadie R, Bhalla RS, Robinson D, Jassal DS. Clinical utility of cardiac magnetic resonance imaging in Churg–Strauss syndrome: case report and review of the literature. *Rheumatol Int* 2009;29:445–9.

2. Blanchard C, Rothenberg ME. Biology of the eosinophil. *Adv Immunol* 2009;101:81–121.
3. Cartin-Ceba R, Keogh KA, Specks U, Sethi S, Fervenza FC. Rituximab for the treatment of Churg–Strauss syndrome with renal involvement. *Nephrol Dial Transplant* 2011; 26:2865–71.
4. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol* 1951;27:277–301.
5. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003;348:1201–14.
6. Donvik KK, Omdal R. Churg–Strauss syndrome successfully treated with rituximab. *Rheumatol Int* 2009;31:89–91.
7. Gotlib J. Eosinophilic myeloid disorders: new classification and novel therapeutic strategies. *Curr Opin Hematol* 2010;17:117–24.
8. Greenan TJ, Grossman RI, Goldberg HI. Cerebral vasculitis: MR imaging and angiographic correlation. *Radiology* 1992;182:65–72.
9. Guillevin L, Cohen P, Mahr A, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum* 2003;49:93–100.
10. Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75:17–28.
11. Heiserman JE, Drayer BP, Keller PJ, Fram EK. Intracranial vascular stenosis and occlusion: evaluation with three-dimensional time-of-flight MR 12. angiography. *Radiology* 1992;185:667–73.
12. Hogan SP, Rosenberg HF, Moqbel R, et al. Eosinophils: biological properties and role in health and disease. *Clin Exp Allergy* 2008;38:709–50.
13. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994;37:187–92.
14. Kahn JE, Grandpeix-Guyodo C, Marroun I, et al. Sustained response to mepolizumab in refractory Churg–Strauss syndrome. *J Allergy Clin Immunol* 2010;125:267–70.
15. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg–Strauss syndrome. *J Allergy Clin Immunol* 2010;125:1336–43.
16. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg–Strauss syndrome. *Medicine (Baltimore)* 1984;63:65–81.
17. 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.
18. Metzgeroth G, Walz C, Erben P, et al. Safety and efficacy of imatinib in chronic eosinophilic leukaemia and hypereosinophilic syndrome: a phase-II study. *Br J Haematol* 2008;143:707–15.
19. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985–93.
20. Pagnoux C, Guilpain P, Guillevin L. Churg–Strauss syndrome. *Curr Opin Rheumatol* 2007;19:25–32.
21. 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;58:586–94.
22. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008;358:1215–28.
23. Sable-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the Churg–Strauss syndrome. *Ann Intern Med* 2005;143:632–8.
24. Saech J, Owczarczyk K, Rosgen S, Petereit H, Hallek M, Rubbert-Roth A. Successful use of rituximab in a patient with Churg–Strauss syndrome and refractory central nervous system involvement. *Ann Rheum Dis* 2010;69:1254–5.
25. Sehgal M, Swanson JW, DeRemee RA, Colby TV. Neurologic manifestations of Churg–Strauss syndrome. *Mayo Clin Proc* 1995;70:337–41.
26. Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg–Strauss syndrome. *Arthritis Rheum* 2005;52:2926–35.
27. Stock KW, Radue EW, Jacob AL, Bao XS, Steinbrich W. Intracranial arteries: prospective blinded comparative study of MR angiography and DSA in 50 patients. *Radiology* 1995;195:451–6.
28. Wadleigh M, Tefferi A. Classification and diagnosis of myeloproliferative neoplasms according to the 2008 World Health Organization criteria. *Int J Hematol* 2010;91:174–9.
29. Zwerina J, Axmann R, Jatzwauk M, Sahinbegovic E, Polzer K, Schett G. Pathogenesis of Churg–Strauss syndrome: recent insights. *Autoimmunity* 2009;42:376–9.