

Case Report

Churg-Strauss syndrome-associated eosinophil-rich cholangitis

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Abstract: Churg-Strauss syndrome (aka eosinophilic granulomatosis with polyangiitis) is characterized by asthma, peripheral eosinophilia and systemic vasculitis. Liver involvement is very rare. We report a case of Churg-Strauss syndrome who presented with asthma, peripheral eosinophilia, cholestatic hepatitis and mononeuropathy multiplex. Paraaortic lymph node biopsy showed marked eosinophilic infiltrate with fibrinoid necrosis of the small vessels and eosinophilic necrotizing granuloma, confirming the diagnosis of Churg-Strauss syndrome. Liver biopsy showed portal inflammation with eosinophil-rich cholangitis and non-necrotizing venulitis. We conclude that this case represents a form of Churg-Strauss syndrome-associated eosinophil-rich cholangitis presenting with cholestatic hepatitis. Churg-Strauss syndrome should be considered in the differential diagnosis in patients presenting with cholestatic hepatitis.

Keywords: Churg-Strauss syndrome, liver, jaundice, cholangitis, vasculitis

Churg-Strauss syndrome (CSS, aka eosinophilic granulomatosis with polyangiitis) was initially described in 1951. It is a small vessel-predominant, systemic necrotizing vasculitis characterized by asthma, hypereosinophilia and necrotizing vasculitis with extravascular eosinophilic granulomas [1]. Although asthma is the defining symptom, extrapulmonary involvement is also common in CSS. Based on the study of the largest CSS series, the common extrapulmonary manifestations include mononeuropathy multiplex (78%), weight loss (71%), paranasal sinusitis (61%), fever (57%), myalgia (54%), skin involvement (51%) and arthralgia (42%) [2]. Gastrointestinal tract involvement occurred in 33% of the patients, with the overwhelming presentation being as abdominal pain, probably due to ischemia secondary to mesenteric vasculitis. Liver involvement in CSS is rare and the most common clinical presentation is abnormal liver function tests, found in only 7% of patients [2]. The histological finding of liver biopsy in CSS patients varies from unremarkable [2, 3] to hepatitis [4] and fibrosis [2]. Vasculitis in the liver is exceedingly rare [2, 3, 5], and there are only a handful cases of bile duct involvement reported in the English litera-

ture [6, 7]. We report a case of CSS presenting with cholestatic hepatitis and eosinophil-rich cholangitis.

Report of a case

A 53-year-old African-American man with a past medical history of hypertension, hyperlipidemia, and gastroesophageal reflux disease initially presented with three months of progressive shortness of breath and was diagnosed with adult-onset asthma. His symptoms improved temporarily following treatment with tapering corticosteroids and montelukast. Two months later he was admitted for worsening shortness of breath. At that time, the patient exhibited acute renal failure, elevated erythrocyte sedimentation rate (ESR) and serum IgE level, marked peripheral eosinophilia, markedly elevated total bilirubin (predominantly direct) and alkaline phosphatase (**Table 1**). He also developed vague abdominal pain, skin rash on the chest and upper extremities, and right hand weakness. An abdominal computed tomography (CT) scan revealed paraaortic lymphadenopathy. At the referring hospital, he underwent a laparotomy with lymph node and liver biop-

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Table 1. Results of key laboratory tests

Laboratory test	At Presentation	On immuno-suppression	Reference range and unit
Peripheral eosinophils	33%	3%	0-5%
	4652	417	0-600 × 10 ⁶ /L
ALT	25	47	15-58 IU/L
AST	24	30	15-40 IU/L
Total bilirubin	26	1.8	0.4-1.4 mg/dL (to convert to μmol/L, multiply by 17.1)
ALP	1800	376	39-117 IU/L
GGT	ND	340	0-65 IU/L
ESR	100	58	< 20 mm/hour
Serum IgE	2456	182	≤ 87 kIU/L

ALT: Alanine transaminase. AST: Aspartate transaminase. ALP: Alkaline phosphatase. GGT: γ-Glutamyl transferase. ND: No data. ESR: Erythrocyte sedimentation rate.

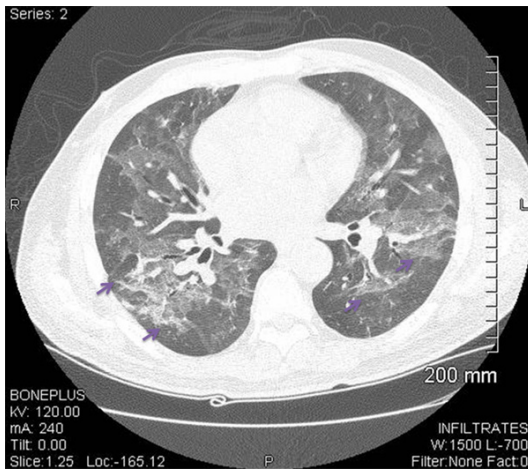


Figure 1. High resolution CT scan of the lungs notable for bilateral patchy ground glass opacities and focal nodularity (arrow).

sies and prednisone were resumed. One week prior to admission the dyspnea recurred upon reduction of prednisone and he was referred to our hospital. He also had occasional subjective fevers and chills, night sweats, a 50-pound weight loss, and cough with mild blood-streaked sputum production. He denied use of tobacco or recent sick contacts. There was no history of allergies. Medications on admission included irbesartan, prednisone, inhaled fluticasone, and albuterol rescue inhaler.

Upon admission, physical examination revealed an acutely ill-appearing man in moderate respiratory distress, with an O₂ saturation of 90% on room air. He was icteric, with significant erythema and injection of the tonsillar pillars. Auscultation of the chest revealed inspiratory and expiratory wheeze with dry crackles in the

apices and a prominent P₂. Abdominal exam was significant for hepatomegaly and tenderness to palpation in the right upper quadrant. There was diminished grip strength in the right median nerve distribution, accompanied by paresthesia. His skin had diffuse palpable purpura on the upper thorax and bilateral upper extremities.

The chest radiograph was unremarkable. Abdominal ultrasound showed hepatomegaly with normal caliber of the common bile duct. High resolution CT scan (without contrast) of the chest revealed bilateral patchy ground glass opacities with areas of nodularity, somewhat more predominant in the apex (**Figure 1**). Pulmonary function test showed mild restriction and moderate reduction in D_LCO (diffuse capacity of the lung for carbon monoxide). Transthoracic echocardiogram showed a normal left ventricle ejection fraction (65%) with moderate right ventricular enlargement.

In addition to the key laboratory results listed in **Table 1**, the patient was found to have mild anemia. Blood and sputum cultures including acid fast stain were all negative for bacteria. Serology tests for viral hepatitis, syphilis, leptospirosis, strongyloides, human immunodeficiency virus, and multiple autoantibodies were negative. Complements (C3 and C4) were slightly reduced. Serum protein electrophoresis was positive for a small M-spike, while urine protein electrophoresis was negative. Immunofixation electrophoresis (IFE) showed two monoclonal IgM lambda and one free kappa chain. Galactomanin (for fungal infection) was negative. Stool was negative for ova, parasite and fecal leukocytes.

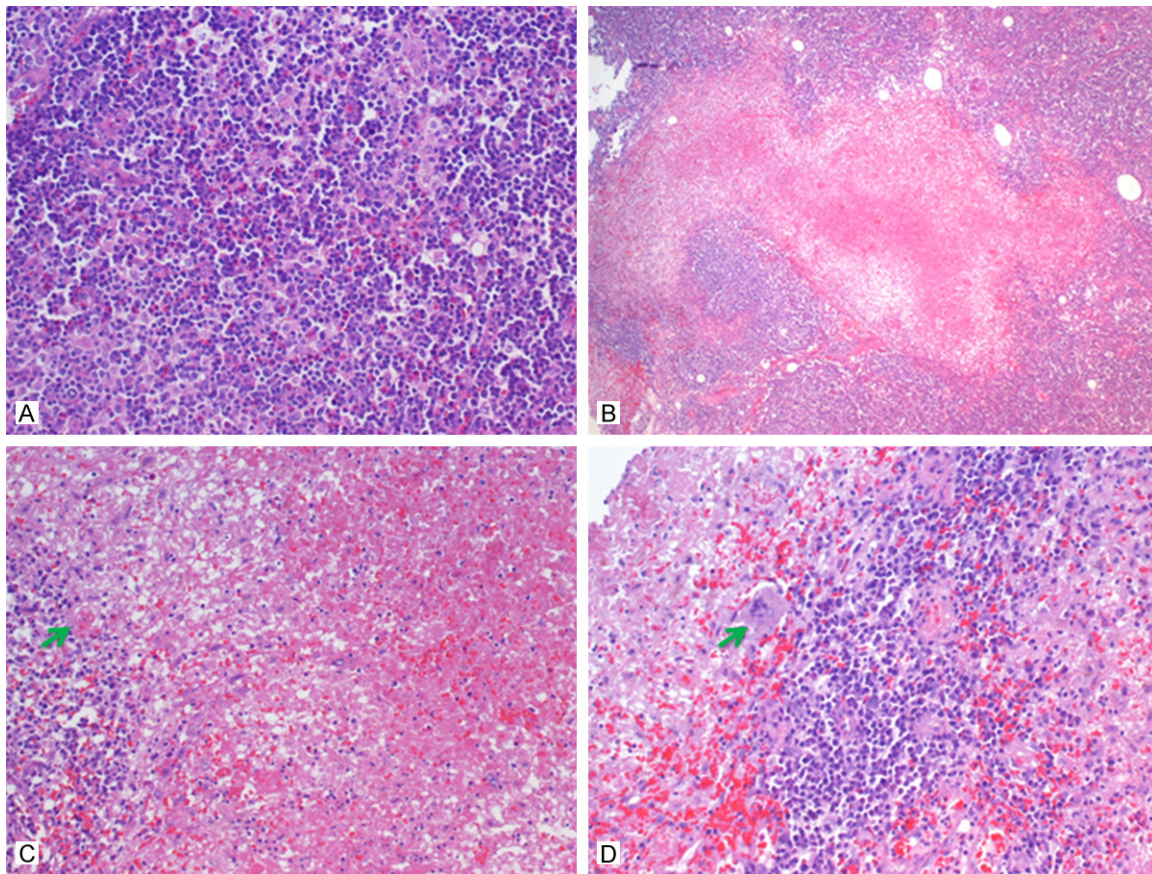


Figure 2. Lymph node biopsy. A. Marked eosinophilic infiltrate in the lymph node (H&E, original magnification $\times 200$). B. Geographic necrotizing granuloma (H&E, original magnification $\times 40$). C. The center of the necrosis is deeply eosinophilic (right upper portion). Fibrinoid necrosis of small vessel is present (arrow) (H&E, original magnification $\times 200$). D. Multinucleated giant cells are present at the edge of the necrotizing granuloma (arrow) (H&E, original magnification $\times 200$).

Review of the lymph node biopsy showed marked eosinophilic infiltration. There was geographic necrotizing granuloma with rare multinucleated giant cells. The center of the necrosis was deeply eosinophilic, and there were small vessels with fibrinoid necrosis (**Figure 2**). The liver biopsy showed expansion of the portal tract with mixed inflammatory infiltrate including many eosinophils and some lymphocytes and plasma cells. The inflammation extended to the bile duct with bile duct damage; however, it did not appear to be duct-centric nor was bile duct destruction identified. Focal eosinophilic non-necrotizing vasculitis of the portal vein was noted. The inflammation was largely limited to the portal tract, with only focal lobular inflammation and minimal interface hepatitis. Focal cholestasis was present at the site of lobular inflammation. Granulomas were not identified (**Figure 3**). A sural nerve biopsy showed perivas-

cular eosinophilic infiltration (figure not shown). The diagnosis of CSS was rendered, and the patient responded well to prednisone and cyclophosphamide, with resolution of most symptoms except for mild residual paresthesia of the hand. At one-year follow-up, he had normal ESR and metabolic profile without anemia or jaundice, though hepatomegaly and intermittent wheezing persisted.

Discussion

CSS is a clinicopathological entity. The American College of Rheumatology proposed six diagnostic criteria (asthma, peripheral eosinophilia, mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrate on radiograph, paranasal sinus abnormality, and biopsy containing a blood vessel with extravascular eosinophils); the presence of four of the six criteria is considered consistent with CSS, with a diag-

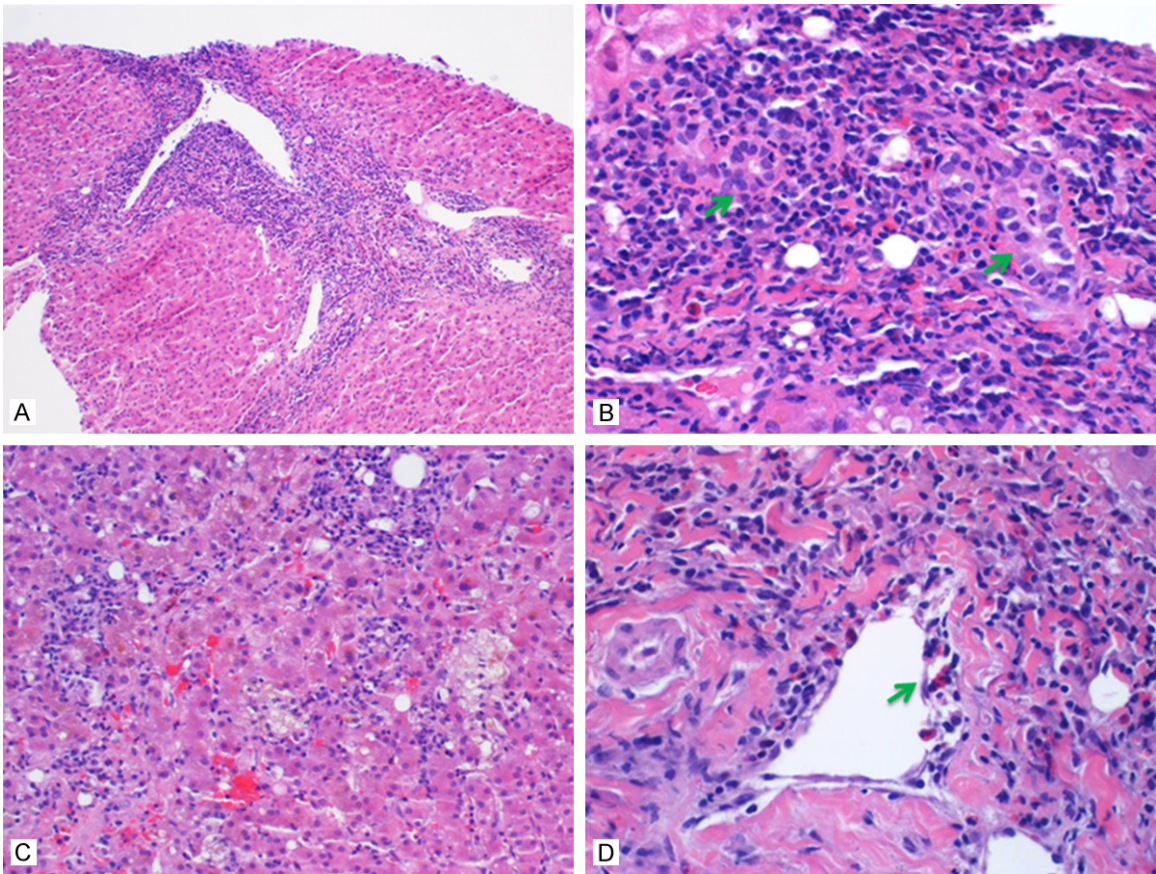


Figure 3. Liver biopsy. A. Mixed portal inflammation without significant interface activity (H&E, original magnification × 100). B. Eosinophil-rich cholangitis (H&E, original magnification × 400). C. Focal lobular inflammation and cholate stasis (H&E, original magnification × 200). D. Eosinophil-rich non-necrotizing vasculitis of the portal vein (H&E, original magnification × 400).

Table 2. CSS cases with obstructive liver disease reported in the literature

#	Author Year	Icteric	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	ALP (U/L)	GGT (U/L)	Antibody	Liver biopsy
1	Conn 1982 [7]	Yes	ND	136	TB: 3.4 DB: 2.4	1486	ND	AMA	Periportal hepatitis and granuloma: PBC
2	Brooklyn 2000 [6]	No	ND	23	TB: 0.5	491	191	ASMA p-ANCA	Bile duct-centric inflammation: granuloma-associated cholangiopathy
3	Bennett 2005 [11]	No	N	N	N	400	400	No	Necrotizing granuloma without vasculitis
4	Yuksel 2008 [4]	No	51	48	TB: 5 DB: 3.7	565	119	RF	Active interface hepatitis
5	Present case	Yes	25	24	TB: 26	1800	340*	No	Portal inflammation with eosinophil-rich cholangitis, and non-necrotizing vasculitis

AMA: anti-mitochondria antibody. ASMA: anti-smooth muscle antibody. ANCA: anti-neutrophil cytoplasmic antibody. RF: rheumatoid factor. TB: total bilirubin. DB: direct bilirubin. N: normal. *After initiation of treatment.

nostic sensitivity of 85% and specificity of 99.7% [8]. The present case meets five of the six proposed criteria, thus compatible with a diagnostic of CSS. Although polyarteritis nodosa, Wegener's granulomatosis and microscopic polyangiitis are often considered as differential diagnoses of CSS, the presence of asthma and

marked eosinophilia makes those three entities very unlikely [9]. Other causes of peripheral eosinophilia such as parasite or fungal infection, allergy, drug sensitivity, and endocrine disorder [10] had been essentially ruled out by the combination of clinical history, physical examination, radiological and laboratory findings.

The presence of peripheral eosinophilia and enlarged lymph node in the present case may suggest a diagnosis of hematologic malignancy, which was initially considered at the referring institution. However, the lymph node biopsy showed no evidence of lymphoma. Rather, there was marked eosinophilic infiltrate with necrotizing small vessel vasculitis and eosinophilic necrotizing granulomas, which are the typical findings in the vasculitic phase of CSS. CSS vasculitis in the liver is very rare, with only one such case noted in the largest CSS series and the type of the vasculitis was not specified in that report [2]. Necrotizing vasculitis was reported in the liver in only two single-case reports [3, 5], and necrotizing granulomas without vasculitis was reported in another [11]. The classic histological findings of CSS are not always present in modern materials [12, 13]. It is now recognized that CSS manifestation depends on the natural history and is also affected by treatment (e.g. corticosteroid therapy); eosinophilic infiltrate and non-necrotizing vasculitis are more common in modern-era CSS cases [12, 14]. The findings in the liver and nerve biopsies of the present case are fully consistent with that notion.

It is intriguing that this case presented with jaundice with obstructive cholestasis on laboratory studies (elevated GGT and ALP). The presence of portal inflammation with bile duct damage in the liver biopsy correlates well with the clinical presentation. Similar laboratory abnormalities have been reported in four other cases in the English literature (**Table 2**). Case #1 had jaundice and positive anti-mitochondria antibody (1:80); in addition, ALP level was markedly elevated to 1486 IU/L. Liver biopsy showed prominent periportal hepatitis with eosinophilic infiltrate and granuloma adjacent to a portal vein, which was interpreted as primary biliary cirrhosis (PBC) [7]. The liver biopsy in case #2 showed portal inflammation with bile duct involvement, and the authors interpreted this as cholangiopathy, possibly associated with granulomatous reaction [6]. Liver biopsy in case #3 showed necrotizing granuloma without vasculitis [11]. Case #4 demonstrated active interface hepatitis [4]. Of note, the GGT/ALP levels were only moderately elevated and no jaundice was mentioned in the three latter cases. Consistent with normal transaminase values, the present case showed no significant

interface hepatitis, and no granulomas were identified in the liver. The portal infiltrate was quite dense and diffuse, in contrast to the mild and patchy nature characteristic of PBC. Although the presence of a few eosinophils is compatible with a diagnosis of PBC, the degree of eosinophilic infiltrate in this case would be very unusual for that entity. The clinical presentation of cholestatic hepatitis in our case is similar to case #1; while the histologic features are more consistent with case #2 in that the bile duct is infiltrated by inflammatory cells accompanied by bile duct damage. The inflammatory cells in our case were not centered on the bile duct as described in case #2 [6], and there was no evidence of associated granuloma in the liver. Although the present case also showed focal lobular hepatitis and some plasma cells, the lack of significant interface hepatitis along with normal transaminases and negative autoimmune serology strongly argue against a diagnosis of autoimmune hepatitis. Taken together, CSS-associated eosinophil-rich cholangitis is the most likely underlying cause in our case.

Low level of M-protein on IFE was present in this case. Various autoantibodies have been identified in CSS patient [2]. Monoclonal gammopathy was previously reported which disappeared upon successful treatment [5]. Whether those M-spikes represent true monoclonal or oligoclonal immunoglobulin is unknown.

In summary, we report a case of CSS with a clinical presentation of cholestatic hepatitis and an unusual histological pattern of bile duct inflammation. We conclude that the eosinophil-rich cholangitis is the underlying cause of cholestatic hepatitis in this case, which was responsive to appropriate immunosuppressive therapy. CSS-associated eosinophil-rich cholangitis should be considered in the differential diagnosis when patients present with hepatic abnormalities.

Disclosure of conflict of interest

None.

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References

- [1] Churg J, Strauss L. Allergic granulomatosis, allergic angitis, and periarteritis nodosa. *Am J Pathol* 1951; 27: 277-301.
- [2] Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999; 78: 26-37.
- [3] Della Rossa A, Baldini C, Tavoni A, Tognetti A, Neglia D, Sambucetti G, Puccini R, Colangelo C, Bombardieri S. Churg-strauss syndrome: clinical and serological features of 19 patients from a single Italian centre. *Rheumatology (Oxford)* 2002; 41: 1286-94.
- [4] Yuksel I, Ataseven H, Basar O, Köklü S, Ertuğrul I, Ibiş M, Temuçin T, Saşmaz N. Churg-strauss syndrome associated with acalculous cholecystitis and liver involvement. *Acta Gastroenterol Belg* 2008; 71: 330-2.
- [5] Gambari PF, Ostuni PA, Lazzarin P, Fassina A, Todesco S. Eosinophilic granuloma and necrotizing vasculitis (Churg-strauss syndrome?) involving a parotid gland, lymph nodes, liver and spleen. *Scand J Rheumatol* 1989; 18: 171-5.
- [6] Brooklyn TN, Prouse P, Portmann B, Ramage JK. Churg-strauss syndrome and granulomatous cholangiopathy. *Eur J Gastroenterol Hepatol* 2000; 12: 809-11.
- [7] Conn DL, Dickson ER, Carpenter HA. The association of Churg-strauss vasculitis with temporal artery involvement, primary biliary cirrhosis, and polychondritis in a single patient. *J Rheumatol* 1982; 9: 744-8.
- [8] Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-strauss syndrome (allergic granulomatosis and angitis). *Arthritis Rheum* 1990; 33: 1094-100.
- [9] Lhote F, Cohen P, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-strauss syndrome. *Lupus* 1998; 7: 238-58.
- [10] Weller PF. Approach to the patient with eosinophilia. UpToDate; 2010.
- [11] Bennett AN, Sangle SR, Jan W, Jenner M, Cavenagh J, Hughes G, D'Cruz DP. Hepatomegaly as a rare presentation of Churg-strauss syndrome. *Rheumatology (Oxford)* 2005; 44: 1458-9.
- [12] Churg A. Recent advances in the diagnosis of Churg-strauss syndrome. *Mod Pathol* 2001; 14: 1284-93.
- [13] Reid AJ, Harrison BD, Watts RA, Watkin SW, McCann BG, Scott DG. Churg-strauss syndrome in a district hospital. *QJM* 1998; 91: 219-29.
- [14] 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.