

# ANCA-negative Churg-Strauss Syndrome: A Case Report

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## Abstract:

A rare and a disease of unknown etiology, Churg–Strauss syndrome (CSS) is a granulomatous necrotizing small vessel vasculitis characterized by the presence of asthma, sinusitis, and hypereosinophilia, which is initially described by Churg and Strauss in 1951. Because of its clinical and pathological features that overlap with those of the other anti-neutrophil antibody (ANCA)-associated systemic vasculitides (AASVs) and now the disease is classified as AASVs. The ANCA status may dictate the clinical phenotype. ANCA-positive patients are significantly more likely to have disease manifestations associated with small-vessel vasculitis, including necrotising glomerulonephritis, mononeuritis and purpura, whereas ANCA-negative cases predominantly likely to have cardiac and lung involvement. The objective of this case report is to point out the possibility of vasculitic rash in ANCA-negative CSS in a 35-year-old man and the disease rarely occurs in Bangladeshi population. We analyze the history, clinical examinations and relevant investigations related to the patient to establish the diagnosis in our department. The clinical scenario and biopsy help us to attain the diagnosis. But due to unavailability of patients' cohort we have limitations of comparison of ANCA status in Bangladeshi populations. Though ANCA-positive and ANCA-negative CSS differ phenotypically, primary therapy for both the conditions is systemic glucocorticoids. Additional immunosuppressive agents like cyclophosphamide, mycophenolate mofetil, azathioprine, rituximab are occasionally added in patients with more advanced or refractory disease.

**Keywords:** Churg–Strauss syndrome, granulomatous necrotizing small vessel vasculitis, hypereosinophilia and asthma, sinusitis, ANCA-negative.

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## Introduction:

Churg–Strauss syndrome (CSS) is a rare small and medium vessel vasculitis characterized by eosinophilic infiltration of organs with necrotizing vasculitis and interstitial and perivascular granulomas<sup>1</sup>. Three phases have been described in the natural history of the disease - prodromal, eosinophilic, and vasculitic phases; although they do not always occur successively<sup>2,3</sup>. The incidence of CSS is about 1-3 per 1000000 populations. Most patients have a prodromal period of many years characterized by allergic rhinitis, nasal polyposis and late-onset asthma that is often difficult to control. The typical acute presentation is with a triad of skin lesions (purpura or nodules), asymmetric mononeuritis multiplex and eosinophilia on a

background of resistant asthma.<sup>4</sup> The ANCA may be negative up to 60% patients of which around 10% are due to low titer antibody levels, a poorly performed IIF or ELISA test.<sup>5</sup> American College of Rheumatology (ACR) has proposed six criteria for CSS—four being necessary for CSS to be diagnosed with 85% sensitivity and 99.7% specificity.<sup>6</sup> The CSS has a long list of differential diagnoses like eosinophilic disorders<sup>7</sup>. The prognostic factors dictate the treatment regimen. Without poor prognostic factors patients is treated only with corticosteroid. The patients with poor prognostic factors need corticosteroids and other immunosuppressants for attaining remission.<sup>8</sup>

## Case Report:

A 35-year-old, man, with history of bronchial asthma for last 3 years, presented to us with the complaints of fever for one and half months, appearance of rashes over both

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for one and half months, appearance of rashes over both lower limbs along with unable to move his right hand for last 7 days due to weakness. Initially he developed low-grade fever, malaise, lassitude, loss of appetite and generalized body-ache. He had lost about 10 kg weight in this period. Ten days prior to admission in Bangabandhu Sheikh Mujib Medical University; he became unable to move his right hand due to weakness without any prior history of local swelling or tenderness; the weakness was associated with burning pain in his hands and feet. Meanwhile, the patient noticed appearance of painful rash in his both lower limbs. The patient had taken anti-asthmatics adequately but symptoms were not subsided. There were no histories suggestive of renal or cardiac involvement. The patient was toxic and febrile. There were multiple erythematous, tender maculopapular and palpable purpuric rashes (Fig: 1 and 2) of different size and shape over both shins. The chest examinations revealed vesicular breath sound with prolong expiration along with rhonchi in both lungs. Right sided wrist and foot drops (Fig: 3) and impaired fine touch sensation in distal parts of all limbs were found. The examinations of other systems were normal.

For diagnosis, relevant investigations were done which showed Hb 8.6 gm/dl, WBC 15000/cmm (Eosinophils 58%), ESR 90 mm at 1st hour. ANA and ANCA were negative. Renal function including urine R/E showed no active sediments, casts and proteinuria. Liver function tests were also within normal. The CXR was unremarkable other than hyperlucency. USG of whole abdomen and echocardiography were also normal. CRP was markedly raised (53.1 mg/l). The nerve conduction velocity revealed motor neuropathy both tibial nerves with absent motor and sensory action potentials over the both peroneal and sural nerves. The skin biopsy specimen was taken from the right shin and histopathological report revealed eosinophilic infiltration in the perivascular region along with presence of chronic inflammatory cells without any granuloma which was consistent with CSS.

#### Discussion:

CSS is an uncommon disease of unknown cause described initially by Churg and Strauss in 1951<sup>9</sup>. Allergic granulomatosis (CSS) is a systemic vasculitis that occurs predominantly in males on a background of chronic asthma and peripheral eosinophilia<sup>10</sup>. Epidemiologic

studies continue to show that CSS is the rarest of the necrotizing small-vessel vasculitides.<sup>11</sup> The mean age at diagnosis of CSS is 40 years which was compatible in our case<sup>12</sup>. Genetic factors may also play a role<sup>13</sup>. Two recent studies on large cohorts of patients have found that ANCA, usually P-ANCA, were present in only 38% of patients. The ANCA status found to dictate the clinical phenotype. ANCA-positive patients are significantly more likely to have disease manifestations associated with small-vessel vasculitis, including necrotising glomerulonephritis, mononeuritis and purpura, whereas ANCA-negative cases more likely to have cardiac and lung involvement.<sup>14</sup> However in our case the patient had no cardiac or lung involvement. The patients ANCA-negative status may be due to low titer antibody levels (in our case the titers are p-ANCA 3.6 U/ml; reference value <6.0 U/ml and c-ANCA 3.0 U/ml; reference value <6.0 U/ml which are done by ELISA method) or laboratory error for example poorly performed IIF or ELISA test; or genuinely ANCA-negative disease.<sup>5</sup> There are several drugs modify the natural course of the disease e.g. leukotriene modifying agents,<sup>15</sup> inhaled glucocorticoids,<sup>16</sup> and omalizumab.<sup>17</sup> American College of Rheumatology (ACR) has proposed six criteria classification for CSS- four being necessary for CSS to be diagnosed with 85% sensitivity and 99.7% specificity<sup>6,1</sup>. (Table-I).

**Table-I**

*ACR Classification Criteria for diagnosis of CSS*

<b>Criterion</b>	<b>Definition</b>
Asthma	History of wheezing or diffuse high-pitched rales on expiration
Eosinophilia	Eosinophilia >10% on white blood cell differential count
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (ie, stocking/glove distribution)
Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness, or radiographic opacification of the paranasal sinuses
Extravascular eosinophils	Biopsy including artery, arteriole, or venule, showing accumulations of eosinophils in extravascular areas

So allergic asthma, rhinosinusitis and eosinophilia is a part of CSS. <sup>18,19</sup> Asthma usually precedes the vasculitic phase by approximately 8 to 10 years <sup>20</sup>. The clinical features develop in simultaneous phases that may not be distinguishable <sup>2,3</sup> (Table-II)

**Table-II***Different phases of CSS with their characteristics*

Phases	Characteristics
Prodromal phase	Atopic disease, allergic rhinitis and asthma. Occurs in 2 <sup>nd</sup> and 3 <sup>rd</sup> decades
Eosinophilic phase	Peripheral blood eosinophilia and eosinophilic infiltration of many organs and commonly seen in lung,
Vasculitic phase	Can have life-threatening sequelae and heralded by constitutional symptoms. Skin involvement common

The "five factors score" guides the severity of vasculitis and initiation of therapy. The "five-factor score" is based on the presence or absence of the following five clinical factors <sup>21</sup>:

- Cardiac involvement
- Gastrointestinal disease (bleeding, perforation, infarction, or pancreatitis)
- Renal insufficiency (plasma creatinine concentration >1.58 mg/dL [141 micromol/L])
- Proteinuria (>1 g/day)
- Central nervous system involvement

But our patient had peripheral neuropathy and transient period of asymptomatic renal involvement. CSS should be distinguish from a group of hypereosinophilic disorders <sup>7</sup>. (Table-III)

**Table-III***Differential Diagnoses of hypereosinophilic disorders*

Hypereosinophilic disorders
Loffler syndrome
Hypereosinophilic syndrome
Eosinophilic gastroenteritis
Chronic eosinophilic pneumonia
Eosinophilic pneumonia

The primary therapy for CSS is systemic glucocorticoids. An additional immunosuppressive agent is added in patients with more advanced or refractory disease and in those whose disease flares with tapering of systemic glucocorticoids. Almost 80 percent of those who achieved a remission required long-term low-dose glucocorticoid therapy <sup>22</sup>.

Cyclophosphamide is given in combination with glucocorticoids for patients with severe or multiorgan disease. <sup>23</sup> The refractory cases may be treated with other options like mycophenolate mofetil, <sup>24</sup> intravenous immune globulin, <sup>25,26</sup> hydroxyurea, <sup>27</sup> azathioprine, <sup>28</sup> rituximab, <sup>29</sup> interferon-alpha, <sup>30</sup> and mepolizumab <sup>31</sup>.

### Conclusion:

Asthma, eosinophilia, and systemic vasculitis are the hallmarks of the CSS. In a case of unusual level of eosinophilia with a history of adult onset asthma, which is difficult to control, there should be high index of suspicion of CSS in our mind in our country even.



**Fig 1:** Maculopapular rashes over medial aspect of left ankle



**Fig 2:** Maculopapular rash over right shin and medial aspect of right ankle



**Fig 3:** Right wrist drop and right foot drop

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