A Case of Churg-Strauss Syndrome Presenting with Foot Drop

Juneth Ria R. Limgenco-Hipe, M.D.*; Bernadette Heizel Manapat-Reyes, M.D.**

Abstract

Background: Churg-Strauss syndrome (CSS), or eosinophilic granulomatosis with polyangiitis, is a rare syndrome that affects small- to medium-sized arteries and veins. Criteria for the diagnosis include: asthma (wheezing, expiratory rhonchi), eosinophilia of more than 10% in peripheral blood, paranasal sinusitis, pulmonary infiltrates (may be transient), histological proof of vasculitis with extravascular eosinophils, and mononeuritis multiplex or polyneuropathy. The worldwide incidence of CSS is approximately 2.5 cases per 100,000 adults per year and its incidence in the United States is one to three cases per 100,000 adults per year.[1] In the Philippines, the exact incidence is unknown with very few published case reports about it.

Setting: University of the Philippines-Philippine General Hospital (UP-PGH), a tertiary training hospital in Manila, Philippines

The Case: A 40-year-old Filipino male with a history of adult onset asthma and recurrent sinusitis manifesting with inability to dorsiflex the left ankle (foot drop), various dermatologic lesions, and arthralgia. Complete blood count showed hypereosinophilia. Electromyography revealed asymmetric moderate to severe sensory and motor denervation of limbs compatible with polyneuropathy. Skin biopsy revealed lymphocytic vasculitis. P-ANCA was positive. During his incumbent hospitalization, the skin lesions, arthralgia and neurologic manifestations improved on administration of high dose steroids. Pregabalin was used to control pain secondary to the mononeuritis multiplex.

Significance: To report a rare case of Churg-Strauss syndrome presenting as foot drop. This case highlights the importance of considering Churg-Strauss syndrome among adult patients presenting with neurologic complaint (inability to dorsiflex the left ankle/foot drop) and various dermatologic lesions.

Keywords: Churg-Strauss syndrome, mononeuritis multiplex, ANCA-associted vasculitis

Introduction

Churg-Strauss syndrome (CSS), or eosinophilic granulomatosis with polyangiitis, is a rare syndrome that affects small- to medium-sized arteries and veins. The worldwide incidence of Churg-Strauss syndrome is approximately 2.5 cases per 100,000 adults per year and its incidence in the United States is one to three cases per 100,000 adults per year.[1] In the Philippines, the exact incidence is unknown but there have been very few published case reports about CSS.

The American College of Rheumatology (ACR) has proposed six criteria for the diagnosis of Churg-Strauss syndrome.[2] The presence of four or more criteria yields a sensitivity of 85% and a specificity of 99.7%. These criteria include (1) asthma (wheezing, expiratory rhonchi), (2) eosinophilia of more than 10% in peripheral blood, (3) paranasal sinusitis, (4) pulmonary infiltrates (may be transient), (5) histological proof of vasculitis with extravascular eosinophils, and (6) mononeuritis multiplex or polyneuropathy.

We report an unusual case of Churg-Strauss syndrome in a 40-year-old Filipino male presenting with inability to dorsiflex the left ankle (foot drop) and various dermatologic lesions.

Case Presentation

A 40-year-old married, Filipino male overseas contract shipworker was admitted for work-up of foot drop. Two months prior to admission, he experienced right knee pain for which he took diclofenac 50mg BID for seven days affording relief. After one week, he noticed that he had gradual swelling, erythema and burning sensation of both feet. He was treated as a case of cellulitis with coamoxiclav 625mg/tab BID and diclofenac 50mg twice a day. After a few

*Fellow in training, Section of Rheumatology, Philippine General Hospital
**Consultant and Faculty, Section of Rheumatology, Philippine General Hospital

Corresponding author: Juneth Ria R. Limgenco-Hipe, MD, Philippine General Hospital, Taft Avenue, Manila, Philippines
Email: junethhipemd@yahoo.com

days, he noted appearance of multiple, pruritic, dark red rashes over his trunk and extremities. He was diagnosed to have "allergic purpura", coamoxiclav was shifted antibiotic to clarithromycin and was given betamethasone cream for his skin lesions but these did not afford relief. After two days, he developed facial edema with appearance of multiple red macules on his fingertips. He was subsequently admitted at a hospital in Saudi Arabia where he was given intravenous dexamethasone affording improvement of facial edema and rashes but the numbness of his left foot progressed to foot drop prompting him to go back to the Philippines.

His past medical history was significant for adult onset asthma diagnosed at 36 years of age requiring maintenance therapy with inhaled corticosteroid (budesonide+formoterol turbohaler), recurrent sinusitis, nasal polyp excision in 2011 and a three-year history of vitiligo on the face and scalp.

On examination the patient had stable vital signs, with essentially normal heart and lung examination. Joint examination showed tenderness of his shoulder and elbow joints without swelling. Skin examination revealed multiple hypopigmented macules and patches on his face and scalp; multiple erythematous plaques over his left ankle and both feet, plantar keratoderma with thick yellowish scaly plaques and onycholysis, onychodystrophy and subungual hyperkeratosis of the toe nails. Neurologic examination revealed sensory deficit of 30% on the lateral aspect of his right thigh and 90% deficit of both feet, also with inability to dorsiflex the left ankle.

Pertinent laboratory findings showed leukocytosis of 33.7 ×109/L and marked eosinophilia at 58%, elevated acute phase reactants ESR 99 mm/h and and C reactive protein of >12mgs/L. Serological tests for hepatitis B and C were negative. (Appendix 1) Electromyography (EMG) revealed asymmetric moderate to severe sensory and motor denervation of limbs compatible with polyneuropathy. (Appendix 2) Echocardiography was unremarkable. (Appendix 3) The working impression then was ANCA-associated vasculitis vs hypersensitivity vasculitis and this was initially managed with hydrocortisone 1.0 mg/kg/day. Pregabalin 75mg/tab BID was used to control neuropathic pain. Dermatologic lesions were managed as follows: methoxalen (oxsoralen) 0.1% cream OD and clobetasol cream HS OD for his vitiligo and terbinafine cream and 3.0% Salicylic acid and 6.0% benzoic acid (Whitfield`s) ointment applied to lesions on his feet (Tinea pedis). There was symptomatic improvement of the neuropathic pain and resolution of joint pains.

On out-patient follow-up, work-ups showed a positive P-ANCA of >600 (APPENDIX 4), negative C-ANCA and negative ANA results. He is now able to ambulate with some assistance. Skin biopsy from lesions on the left ankle and foot showed lymphocytic vasculitis. Overall the findings were consistent with ANCA-associated vasculitis.

Discussion

We are presented with a 40-year-old Filipino male with a history of adult onset asthma and recurrent sinusitis manifesting with inability to dorsiflex the left ankle (foot drop), various dermatologic lesions, and arthralgia. Complete blood count showed hypereosinophilia. Electromyography revealed asymmetric moderate to severe sensory and motor denervation of limbs compatible with polyneuropathy. Skin biopsy revealed lymphocytic vasculitis. P-ANCA was positive. During his incumbent hospitalization, the skin lesions, arthralgia and neurologic manifestations improved on administration of high dose steroids. Pregabalin was used to control pain secondary to the mononeuritis multiplex.

History and Diagnosis

It was in year 1951 when pathologists Jacob Churg and Lotte Strauss reported "fever, hypereosinophilia, symptoms of cardiac failure, renal damage, and peripheral neuropathy, resulting from vascular embarrassment in various systems of organs"[3] in a series of thirteen patients with necrotizing vasculitis previously diagnosed as "periarteritis nodosa", accompanied by hypereosinophilia and severe asthma.[3] Churg and Strauss noted three features which distinguished their patients from other patients with periarteritis nodosa but without asthma: necrotizing vasculitis, tissue eosinophilia, and extra vascular granuloma.[4] As a result, they proposed that these cases were evident of a different disease entity, which they referred to as "allergic granulomatosis and angiitis".[4]

The exact cause of this allergic angiitis and granulomatosis is still unknown4. No data have been reported regarding the role of immune complexes or cell-mediated mechanisms in this disease, although autoimmunity is evident with the presence of hypergammaglobulinemia, increased levels of immunoglobulin E (IgE), rheumatoid factor, and ANCA. HLA-DRB4 positivity may be a genetic risk factor for the development of Churg-Strauss syndrome and may increase the likelihood of vasculitic manifestations of the disease[5].

The clinical features of Churg-Strauss Syndrome (CSS) typically develop in several sequential phases, although these phases are not always clearly distinguishable.[6-7] The prodromal phase is characterized by airway inflammation presenting with allergic rhinitis and asthma. The second phase is marked by the presence of eosinophilic infiltrative disease which include peripheral blood eosinophilia and eosinophilic

infiltration of multiple organs, especially the lung and gastrointestinal tract. Finally, the third and final phase, which can be life threatening, consists of systemic medium- and small-vessel vasculitis with granulomatous inflammation. The vasculitic phase may be heralded by nonspecific constitutional symptoms and signs, especially fever, weight loss, malaise, and lassitude. This phase usually develops within 5 years of the onset of asthma, although it may be delayed for several decades. The patient had four years history of asthma before he manifested with CSS.

In a retrospective case series of 96 patients done by Guillevin et al (1999), the following are the most common manifestations and findings of CSS: asthma was the most frequently observed presenting manifestation (97%). This was followed by mononeuritis multiplex (77%), allergic rhinitis (61%), skin manifestations (49%) and arthralgias (40%).[8] All of which are present in our patient upon admission. Necrotizing vasculitis mediated by cytotoxic T cells leading to ischemia, appears to be the major cause of the neuropathy. This may progress into asymmetrical polyneuropathy that is restricted to the limbs.[9] Electromyography and nerve conduction velocity studies were performed in our patient which revealed moderate to severe sensory and motor denervation of limbs in an asymmetrical manner. Findings indicate the presence of axonal dysfunction. These findings are compatible with a polyneuropathy of various etiologies.

Tissue biopsy is the gold standard for the diagnosis of Churg-Strauss.[10] The characteristic pathologic changes in CSS, found especially in the lung,[11-12] include small necrotizing granulomas, as well as necrotizing vasculitis involving small arteries and venules. The granulomas are composed of a central eosinophilic core surrounded radially by macrophages and epithelioid giant cells. There are surprisingly few detailed pathologic descriptions of the lung findings in Churg-Strauss syndrome. Part of the problem is that tissue biopsy is not necessary for diagnosis in every case, and sites other than lung (especially skin, muscle, and nerve) are sampled more often. For example, only two of 39 biopsies in the series reported by Chumbley et al[13] and two of 25 in the series by Guillevin et al.[8] were taken from lung. In one retrospective case series involving 90 patients with Churg-Strauss syndrome, 29 patients who underwent skin biopsy showed extravascular necrotizing granuloma (15 specimens) and leukocytoclastic vasculitis (16 specimens).[14] The latter finding was seen in our patient.

Based on the American College of Rheumatology criteria for the diagnosis of CSS, we describe a patient who presented with five hallmark features of Churg-Strauss syndrome: history of asthma, recurrent sinusitis, pulmonary infiltrate, eosinophilia, mononeuritis multiplex and skin biopsy revealing lymphocytic vasculitis The criteria requires at least four of the six to diagnose CSS with a sensitivity of 85% and a specificity of 99.7%.[2]

The identification of antineutrophil cytoplasmic antibodies (ANCA)[15] provided a sensitive, although nonspecific, marker for a particular group of systemic vasculitides including CSS. ANCA with a cytoplasmic staining pattern (cANCA), largely specific for the immunogenic epitopes of antiproteinase[3], was shown to have 98% sensitivity and high specificity for active clinically identified cases of Wegener granulomatosis.[16] ANCA with a perinuclear staining pattern (pANCA) was also identified and shown to have antigenic specificity for epitopes expressed by myeloperoxidase (MPO) as well as other possible epitopes. pANCA is an important marker for Churg-Strauss Disease.[17] The test for p-ANCA in this patient is positive. ANCA provides considerable value in supporting the diagnosis of clinically classified ANCA-related illnesses.

Treatment and Prognosis

Treatment regimen is based on Five Factor Score (FSS) highlighting organ involvement.[18] FFS includes the following five factors: 1. Cardiac involvement, 2. Gastrointestinal (GI) disease (bleeding, perforation, pancreatitis), 3. Renal insufficiency (Creatinine > 1.6 mg/dl), 4. Proteinuria (> 1gm/day) and 5. Central nervous system (CNS) involvement (mononeuritis, polyneuropathy). An FFS of 0 connotes a 12% five year mortality rate; FFS of 1, a 26% five-year mortality rate and FFS >3, 46% five-year mortality rate. Prognosis with current series is encouraging with survival rate of 70% at five years.[8] This patient has an FSS of 1 (CNS involvement) and no cardiac or GI involvement, thus a fairly good prognosis.

Glucocorticoids alone are usually adequate for the treatment of CSS.[19] In this patient, intravenous hydrocortisone at 1.0 mg/kg/day was started as treatment for the vasculitis, which was later shifted to methylprednisolone. He was also given topical creams and ointments for his skin lesions. This patient was also advised to continue his medication for his asthma. Cytotoxic drugs are necessary in fewer than 20% of patients. Major life-threatening organ involvement may require treatment with pulse doses of intravenous corticosteroids and other cytotoxic agents. Cyclophosphamide, an alkylating agent is typically given in intravenous pulses for three months then patients are maintained with either oral mycophenolate or azathioprine. Plasma exchange has been studied in Churg-Strauss syndrome and other ANCA-positive vasculitides without a clear benefit.[20] Although it has not improved the course of the disease, plasma exchange has been used but has not added benefit to the treatment of patients who were treated with prednisone or cyclophosphamide.

This is based on a meta-analysis of 140 patients with glomerulonephritis and Churg-Strauss syndrome and microscopic polyangiitis.[20] The search for new therapies is in progress. ANCA-positivity led to the use of rituximab in a few patients, with some reported efficacy, at least at short term and on eosinophil counts.[21-22]

Conclusion

The case of a 40-year-old Filipino male with four years history of adult onset asthma and recurrent sinusitis subsequently showing manifestations of a systemic vasculitis was presented. In this patient, the vasculitis presented four years after the onset of asthma as various dermatologic lesions and neuropathy, with first symptom of sensory deficits progressing to foot drop at the left. Fulfilling the ACR criteria, a positive p-ANCA and skin biopsy established the diagnosis of CSS in this patient. He had good response to corticosteroid treatment, with symptoms starting to improve in less than two days after initiation of steroids. When physicians encounter cases of adult onset asthma with other clinical manifestations like foot drop and hypereosinophilia are present, they have to consider the possibility of CSS.

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APPENDIX 1

LABORATORY RESULTS

	8/29/2013	8/30/2013	8/31/2013
CBC Hgb	135		132
Hct	0.416		0.391
WBC	33.70		31.58
Platelet	637		646
Neutrophils	30		27
Lymphocytes	9		12
Monocytes	3		3
Eosinophils	58		57
ESR	23	99 (Westergreen method)	38
Sodium	131		
Potassium	4.4		
Chloride	91		
RBS	4.0		
Creatinine	66		
Albumin	27		
Calcium	2.04		
Cholesterol	3.48		
AST	33		
ALT	42		
CRP		>12	
HbsAg		Nonreactive	
Anti-Hbc total		Nonreactive	
Anti-HCV		Nonreactive	
Urinalysis	Normal		

APPENDIX 2

ELECTROMYOGRAPHY

August 30, 2013

NSS

1. No sensory nerve action potentials could be recorded from the sural nerves. SNAP amplitudes of the median, ulnar and radial nerves were normal
2. Sensory latencies and nerve conduction velocities of elicited SNAPs were normal.
3. Amplitudes of the compound muscle action potentials of the peroneal and tibial nerves were reduced. CMAP amplitudes of the median and ulnar nerves were normal.
4. Motor latencies and nerve conduction velocities of elicited CMAPs were normal.
5. No F-wave could be recorded from the right tibial, right and left peroneal nerves.

EMG

Monopolar needle studies were done on selected muscles of the upper and lower extremities. An increase in insertional activity and the presence of fibrillation potentials/ positive sharp waves were seen in most muscles tested. A reduction in recruitment was recorded in all muscles tested.

Interpretation:

Today's electrodiagnostic examination revealed moderate to severe sensory and motor denervation of limbs tested in an asymmetrical manner. Findings indicate the presence of axonal dysfunction. These findings are compatible with a polyneuropathy of various etiologies such as toxic metabolic including vasculitic. Please correlate clinically.

APPENDIX 3

ECHOCARDIOGRAPHY

September 2, 2013

Ejection Fraction: 61%

Normal sized left ventricle with concentric remodelling with good wall motion and contractility and preserved overall systolic function
Normal sized left atrium, right atrium and right ventricle
Doppler evidence of diastolic relaxation abnormality grade 1
Aortic valve sclerosis
Pulmonic regurgitation
Normal pulmonary artery pressure

APPENDIX 4

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)

Date received: 8/30/2013		Date released: 9/3/2013
P-ANCA	>600 (Positive)	Negative: <7 U/ml Equivocal 7-10 U/ml Positive: >10 U/ml
C-ANCA	0.5 (negative)	Negative <7 U/ml Equivocal 7-10 U/ml Positive: >10 U/ml