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CLINICAL VIGNETTE

"Barely Survived: A Case of Eosinophilic Granulomatosis with Polyangiitis Leading to End Stage Kidney Disease and Sequellae Despite Treatment"

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A 76-year-old male with a past medical history of chronic maxillary sinusitis complicated by nasal polyps developed malaise and weakness ongoing for a month. He also complained of bilateral jaw and neck pain, and ongoing sinus pressure. He denied recent chills, chest pain, dyspnea, dysuria or fevers. His temperature was 36.8 degrees C, blood pressure 131/71 mmHg, pulse 89 bpm, respiratory rate 18, and his pulse oximeter saturation was 97% on room air. Physical exam was just notable for peri-orbital swelling, otherwise normal. Initial labs showed a serum sodium of 135 mmol/L, potassium 4.5 mmol/L, total CO2 28 mmol/L, BUN of 17 mg/dl, and creatinine of 1.3 mg/dl. His WBC was 14,900 cells/ul, Hgb 15.3 g/dl, and platelets 230,000 cells/ul. CT of the head and brain showed sinus mucosal thickening and he was sent home with a course of Amoxicillin/clavulanate. Subsequently an ENT physician recommended sinus surgery. He continued to feel poorly, with worsening malaise and mild dyspnea. This progressed to anorexia and decreasing oral intake. He reported a fever at home of 102º F. His symptoms progressed with difficulty ambulating and weakness in his lower extremities and he presented to his primary doctor. Labs showed a serum creatinine of 2.1 mg/dl. His symptoms progressed and he eventually presented to the emergency department. His serum creatinine had increased to 8.2 mg/dl and BUN 95 mg/dl. Serum sodium was 127 mg/dl. Serum total CO2 was 16, and serum potassium was 5.8. His WBC was 11.7, Hgb 13.6, platelets 242. Differential showed neutrophil 78.2%, lymphocytes 5.4%, monocytes 6.7%, and eosinophils 9.5%. His urine analysis was notable for 1+ blood, 1+ protein, 771 RBCs/ul, 10 WBCs/ul. Urine protein-creatinine-ratio was 1.1. FENA was 6.9%. He was given a 500 cc bolus of normal saline, and continued @ 100cc/hr. His kidney function continued to worsen and hemodialysis was initiated. Subsequently his C-ANCA came back positive at 1:160 titer, myeloperoxidase positive at 99 units, P-ANCA positive at 1:640 titer and proteinase-3 ab negative. ANA was negative and rheumatoid factor positive at 277 IU/ml. Sedimentation rate was 29. A kidney biopsy showed mixed infiltrate of inflammatory cells including numerous eosinophils and rare giant cells. No glomeruli were seen on light or immunofluorescence microscopy. Electron microscopy showed a medium-sized artery with transmural fibrinoid necrosis and surrounding granulomatous inflammation, consistent with an ANCA-associated necrotizing vasculitis.

Given the acute kidney injury, positive ANCA serologies, peripheral eosinophilia and kidney biopsy showing granulomatous necrotizing vasculitis, a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) or Churg-Strauss vasculitis was made. He was started on methylprednisolone 1000 mg daily for 3 days, then switched to prednisone 60 mg daily. Cyclophosphamide 50 mg po daily was started. The dose was increased to 100 mg daily after three days. On the 12th day of hospitalization, the patient continued to require hemodialysis. He received a trial of five plasma exchange sessions with no response. He developed pancytopenia and mucositis from cyclophosphamide, so this was switched to rituximab. His kidney function never improved and he had a prolonged hospitalization complicated by recurrent bouts of atrial fibrillation, hypotension, and weakness resulting in severely limited mobility. He was eventually discharged on three times weekly hemodialysis. Over the past two years since discharge, he has gradually regained strength, though continues to suffer from generalized weakness and still needs to use a walker and remains underweight.

EGPA is a necrotizing small vessel vasculitis with prominent eosinophilic infiltrates on biopsy and most commonly arises in individuals with a history of asthma.[1] The prevalence in general population studies worldwide is reported at 10.7-13 cases per million and incidence is 0.5-6.8 cases per million per year, though the incidence is higher for asthma patients with 34.6-67.4 cases per million per year.[2] A recent study reports an incidence of EGPA of 4 per million per year in Olmsted County MN.[3]

The initial inducing events of autoimmunity and many details about the pathogenesis of EGPA are incompletely understood. However, substantial evidence has recently accumulated about the type of immune reaction which occurs in this disease. T cell activation by the Th2 pathway is a hallmark of EGPA.[4] The associated cytokines of IL2, IL5, IL10, IL13, and the T cell surface marker CD294, are elevated in peripheral T cell lines, sinus biopsies, and bronch-alveolar lavage fluid from patient with EGPA.[4] However, elevated amounts of Th17 T cells, IL17, Th1 T cells, and reduced T regulatory cells have also been seen in patients with EGPA.[5] The chemokine eotaxin-3 (CCL26), produced by endothelial cells and inflammatory cells, causes chemotaxis and activation of eosinophils and is markedly elevated in affected sites in patient with EGPA, and is a potential biomarker of disease.[6] Finally, evidence for B cell

involvement includes the observations that 30-40% of patients have antineutrophil cytoplasmic antibody (ANCA),[7] and that more severe disease responds to cyclosphosphamide, which is relatively B-cell specific and rituximab.[8]

EGPA is a multisystem disease and often occurs with a prodromal phase characterized by years of asthma and constitutional symptoms, an eosinophilic phase, and finally a vasculitic phase.[1] ANCA is seen in 31-37% of patients, mostly in the form of MPO-ANCA.[7,9] About 50% of patients with ANCA have renal disease and about half of patients with renal involvement have pauci-immune rapidly progressive glomerulonephritis.[7,10] Churg and Strauss proposed diagnostic criteria in 1951, and there have been subsequent criteria by Langham in 1984 and the American College of Rheumatology in 1990. They all require asthma, eosinophilia, and tissue vasculitis.[1] Commonly affected organs other than the lungs and kidneys include sinuses, mononeuritis, polyneuropathy, myocarditis, pericarditis, GI tract, skin, and arthralgias/myalgias.[9,11]Vasculitis activity can be standardized with the Birmingham Vasculitis Activity Score and other systems, and the Five Factor score is most commonly used for prognosis.[12] This scoring system was developed in a French cohort of 342 patients and found that the following factors increased mortality: proteinuria > 1g per day; serum creatinine > 1.58, GI involvement defined as bleeding, perforation, infarction, or pancreatitis; CNS involvement; cardiomyopathy. Six year survival was 86.1%, 69.4%, and 47% for a FFS of 0, 1, and 2 respectively.[13]

The first line of treatment for EGPA is corticosteroids at 1mg/kg/d for 2-3 weeks followed by gradual tapering to ensure control of disease.[14] For patients without poor prognostic factors (ie FFS 0), the rate of remission with corticosteroids alone was 93%, though the relapse rate was high at 35% in the French Vaculitis Study Group.[15] Patients with more severe disease benefit from the addition of cytotoxic therapy, for example those with a FFS $\geq$2 in a long-term followup study did better with cyclosphosphamide compared to corticosteroids alone.[16] This group subsequently showed patients with CSS and at least one adverse prognostic factor, cyclophosphamide 0.6g/m2 IV every 2 weeks x 2 doses and then monthly for a total of 12 pulses had a similar efficacy and toxicity but lower risk of relapse than a total of 6 pulses.[17] More recently, a small open-label pilot study with rituximab given at 375mg/m2 weekly x 4 doses achieved a renal remission in all three patients.[18]

Though treatment is usually successful at achieving remission, challenges remain with relapses and sequellae. A prospective study of 118 patients found that of 115 who achieved a first remission, there was a mean relapse rate of 41% at a mean 26 months post treatment onset. Sequellae included asthma (83%), peripheral neuropathy (45%), nasal blockage/chronic discharge (35%), and osteoporosis (30%). MPO-ANCA positivity at diagnosis was strongly associated with risk of relapse.[19]

This patient's case was unusual for EGPA in that he did not have a prominent history of asthma and unfortunately, his kidney disease did not respond meaningfully to the cytotoxic therapy. Like many cases of vasculitis, he presented with an insidious onset and the treatment might have been received too late to impact the kidneys. He suffered from both toxicity of treatment and likely sequellae of myopathy, though after two years on dialysis and off treatment, his health status has slowly improved.

REFERENCES

1. **Greco A, Rizzo MI, De Virgilio A, Gallo A, Fusconi M, Ruoppolo G, Altissimi G, De Vincentiis M.** Churg-Strauss syndrome. *Autoimmun Rev.* 2015 Apr;14(4):341-8. doi: 10.1016/j.autrev.2014.12.004. Epub 2014 Dec 11. Review. PubMed PMID:25500434.
2. **Mouthon L, Dunogue B, Guillevin L.** Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). *J Autoimmun.* 2014 Feb-Mar;48-49:99-103. doi: 10.1016/j.jaut.2014.01.018. Epub 2014 Feb 12. Review. Erratum in: *J Autoimmun.* 2014 Dec;55:94. PubMed PMID: 24530234.
3. **Berti A, Cornec D, Crowson CS, Specks U, Matteson EL.** The Epidemiology of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis in Olmsted County, Minnesota: A Twenty-Year US Population-Based Study. *Arthritis Rheumatol.* 2017 Dec;69(12):2338-2350. doi: 10.1002/art.40313. Epub 2017 Nov 9. PubMed PMID: 28881446; PubMed Central PMCID: PMC-5711593.
4. **Vaglio A, Buzio C, Zwerina J.** Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. *Allergy.* 2013 Mar;68(3):261-73. doi: 10.1111/all.12088. Epub 2013 Jan 18. Review. PubMed PMID: 23330816.
5. **Jakiela B, Sanak M, Szczeklik W, Sokolowska B, Plutecka H, Mastalerz L, Musial J, Szczeklik A.** Both Th2 and Th17 responses are involved in the pathogenesis of Churg-Strauss syndrome. *Clin Exp Rheumatol.* 2011 Jan-Feb;29(1 Suppl 64):S23-34. Epub 2011 May 11. PubMed PMID: 21470488.
6. **Zwerina J, Bach C, Martorana D, Jatzwauk M, Hegasy G, Moosig F, Bremer J, Wieczorek S, Moschen A, Tilg H, Neumann T, Spriewald BM, Schett G, Vaglio A.** Eotaxin-3 in Churg-Strauss syndrome: a clinical and immunogenetic study. *Rheumatology (Oxford).* 2011 Oct;50(10):1823-7. doi: 10.1093/rheumatology/keq445. Epub 2011 Jan 25. PubMed PMID: 21266446.
7. **Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, Sinico RA, Sivasothy P, Wechsler ME, Groh M, Marchand-Adam S, Khouatra C, Wallaert B, Taillé C, Delaval P, Cadranel J, Bonniaud P, Prévot G, Hirschi S, Gondouin A, Dunogué B, Chatté G, Briault C, Pagnoux C, Jayne D, Guillevin L, Cordier JF; Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERM"O"P).** Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): A study of 157 patients by the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and the European Respiratory Society Taskforce on eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Autoimmun Rev.* 2017 Jan;16(1):1-9. doi: 10.1016/j.autrev.2016.09.018. Epub 2016 Sep 23. PubMed PMID: 27671089.

8. **Mohammad AJ, Hot A, Arndt F, Moosig F, Guerry MJ, Amudala N, Smith R, Sivasothy P, Guillevin L, Merkel PA, Jayne DR.** Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Ann Rheum Dis.* 2016 Feb;75(2):396-401. doi: 10.1136/annrheumdis-2014-206095. Epub 2014 Dec 2. PubMed PMID: 25467294.
9. **Tsurikisawa N, Oshikata C, Kinoshita A, Tsuburai T, Saito H.** Longterm Prognosis of 121 Patients with Eosinophilic Granulomatosis with Polyangiitis in Japan. *J Rheumatol.* 2017 Aug;44(8):1206-1215. doi: 10.389 9/jrheum.161436. Epub 2017 Jun 1. PubMed PMID: 285 72468.
10. **Sinico RA, Di Toma L, Maggiore U, Tosoni C, Bottero P, Sabadini E, Giammarresi G, Tumiati B, Gregorini G, Pesci A, Monti S, Balestrieri G, Garini G, Vecchio F, Buzio C.** Renal involvement in Churg-Strauss syndrome. *Am J Kidney Dis.* 2006 May;47(5):770-9. Pub Med PMID: 16632015.
11. **Clutterbuck EJ, Evans DJ, Pusey CD.** Renal involvement in Churg-Strauss syndrome. *Nephrol Dial Transplant*. 1990;5(3):161-7. PubMed PMID: 2113641.
12. **Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P;** French Vasculitis Study Group (FVSG). The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine (Baltimore).* 2011 Jan;90(1):19-27. doi: 10.1 097/MD.0b013e318205a4c6. PubMed PMID:21200183.
13. **Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Casassus P.** Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore).* 1996 Jan;75(1):17-28. PubMed PMID: 8569467.
14. **Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, Cottin V, Dalhoff K, Dunogué B, Gross W, Holle J, Humbert M, Jayne D, Jennette JC, Lazor R, Mahr A, Merkel PA, Mouthon L, Sinico RA, Specks U, Vaglio A, Wechsler ME, Cordier JF, Guillevin L.** Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med.* 2015 Sep; 26(7):545-53. doi: 10.1016/j.ejim.2015.04.022. Epub 2015 May 9. PubMed PMID: 25971154.
15. **Ribi C, Cohen P, Pagnoux C, Mahr A, Arène JP, Lauque D, Puéchal X, Letellier P, Delaval P, Cordier JF, Guillevin L;** French Vasculitis Study Group. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum*. 2008 Feb;58(2):586-94. doi: 10.1002/art.23198. PubMed PMID: 18240234.
16. **Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, Jarrousse B;** French Vasculitis Study Group. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum.* 2001 Mar;44(3):666-75. PubMed PMID:11263782.
17. **Cohen P, Pagnoux C, Mahr A, Arène JP, Mouthon L, Le Guern V, André MH, Gayraud M, Jayne D, Blöckmans D, Cordier JF, Guillevin L;** French Vasculitis Study Group. Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Rheum.* 2007 May 15;57(4):686-93. PubMed PMID: 17471546.
18. **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 Sep;26(9):2865-71. doi: 10.1093/ndt/gfq852. Epub 2011 Feb 16. PubMed PMID: 21325353; PubMed Central PMCID: PMC3218640.
19. **Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Stern M, Pagnoux C, Mouthon L, Guillevin L;** French Vasculitis Study Group. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. *J Autoimmun.* 2013 Jun;43:60-9. Doi:10.1016/j.jaut.2013.03.003. Epub 2013 Apr 13. PubMed PMID: 23590801.

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