RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Mystery Case: Diagnostic challenges in a young patient with hypereosinophilia

Jorge G. Ortiz, MD
Preston W. Douglas, MD
Chandler E. Gill, MD
Swati Mehrotra, MD
José Biller, MD

Correspondence to
Dr. Ortiz:
jorge.ortizgarcia@uchospitals.edu

SECTION 1

A 48-year-old woman with recent diagnosis of nonischemic cardiomyopathy and longstanding history of asthma and allergic rhinitis without additional vascular risk factors had intermittent chest pain and dyspnea for 6 weeks, treated with antibiotics and oral steroids without benefit. Subsequently, she developed bilateral leg edema, orthopnea, and chest pain, and was hospitalized twice at another institution. Transthoracic echocardiogram (TTE) demonstrated an ejection fraction (EF) of 30%. Cardiac catheterization was normal. CT of the chest showed a large pericardial effusion (~300 mL) and bilateral pleural effusions. She had urgent pericardiocentesis and right thoracentesis, and was transferred to our institution for further evaluation and care.

Admission ancillary blood tests showed a C-reactive protein of 12.3 mg/dL and erythrocyte sedimentation rate of 38 mm/h. Leukocyte count was 15.2 K/UL with 30% eosinophils (EO%). Subsequent blood count showed a leukocyte count of 13.0–12.3 to 11.5–13.6 K/UL and EO 33–34 to 29%–31%, respectively.

On the day of admission, the patient had an episode of blurriness of the right half of her visual field that was further restricted to right upper visual field blurriness. Soon thereafter, she had a migrating right hemibody numbness beginning on her right foot, propagating to the right side of her face. The whole episode lasted 5 minutes, and resolved spontaneously without sequela. Neurologic examination conducted 3 days after index neurologic event was normal.

Question for consideration:

1. Where would you localize the neurologic deficit?

GO TO SECTION 2

From the Departments of Neurology (J.G.O., P.W.D., C.E.G., J.B.) and Pathology (S.M.), Stritch School of Medicine, Loyola University Chicago, IL.
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

© 2017 American Academy of Neurology

© 2017 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

SECTION 2

Our patient most likely experienced a homonymous hemianopia consistent with a contralateral retrochiasmatic lesion. Homonymous hemianopia results from lesions of the occipital lobe (~40%), parietal lobe (~30%), temporal lobe (~25%), or optic tract and lateral geniculate body (~5%).[1]

The associated transient right-sided paresthesias further narrow the anatomic localization to the left posterior parieto-occipital cortex.

Question for consideration:

1. What is your differential diagnosis and what further investigations would you recommend?

GO TO SECTION 3

© 2017 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Differential diagnosis includes TIAs or ischemic stroke with rapidly improving deficits; seizures; migrainous phenomena; or amyloid spells, the latter characterized by spreading negative (weakness/numbness) and positive (paresthesias) manifestations of brief duration (seconds to minutes) described in some patients with cerebral amyloid angiopathy.[2]

Our patient had a history of asthma and evidence of involvement of at least 2 systems, namely nonischemic cardiomyopathy with depressed EF and bilateral pleural and pericardial effusions. The presence of marked blood eosinophilia was a key clinical clue. Diagnostic considerations in patients presenting with multiorgan system dysfunction in the presence of eosinophilia include the following:

1. Eosinophilic granulomatosis with polyangiitis (EGPA)
2. Certain infectious disorders, such as coccidiomycosis or filarial infection by the nematodes *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori*
3. Loeffler endocarditis, a form of eosinophilic myocarditis associated with endomyocardial fibrosis and recurrent thromboembolic events linked to eosinophilic leukemia, carcinoma, lymphoma, or infections
4. Hypereosinophilic syndrome, characterized by persistent blood and bone marrow eosinophilia with involvement of one or more organ systems (most commonly heart, skin, CNS, gastrointestinal system, or spleen) in the absence of a more definitive diagnosis

A thorough history and physical examination, including detailed skin examination, are the most important first steps to further narrow the differential diagnosis. In terms of diagnostic testing, MRI was helpful in determining whether an ischemic or infiltrative CNS disease was present. Transbronchial biopsies from the left upper and right lower lobes demonstrated a dense eosinophilic infiltrate with necrotic debris. Bone marrow biopsy was performed to rule out a primary hematologic process, and showed hypereosinophilia (31%) but otherwise normal cell morphology (figure, D).

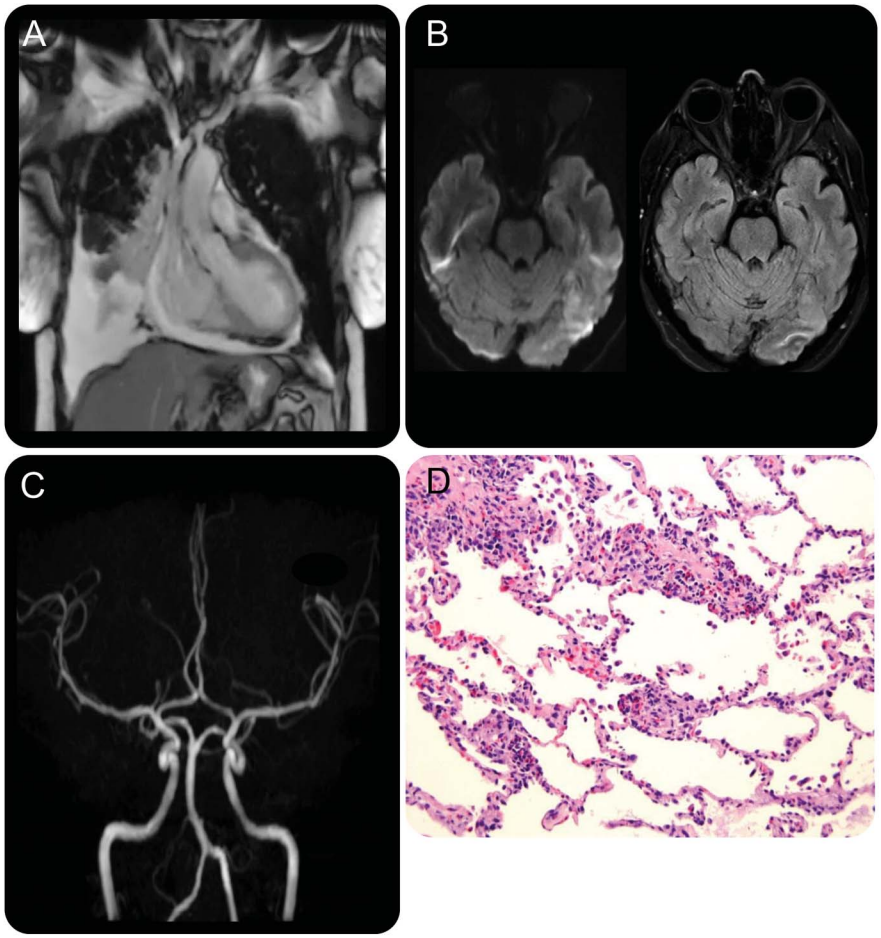
Immunoglobulin E was 331 IU/mL. Other ancillary investigations including antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibody (ANA), rheumatoid factor, and complement C3 C4 were normal. Infectious workup was negative for *Aspergillus*, *Blastomyces*, *Coccidiodes*, *Cryptococcus*, *Histoplasma*, *Strongyloides*, and HIV antibodies, and hepatitis A, B, C panel was unremarkable. Follow-up TTE showed mild systolic dysfunction with an EF of 45% and a small pericardial effusion. Cardiac MRI demonstrated patchy fibrosis of the basal and inferior septum suggestive of myocarditis with an EF of 28.9% (figure, A). Brain MRI demonstrated an irregular area of restricted diffusion-weighted image (DWI) in the posterior left temporo-parieto-occipital region indicative of subacute ischemia. There was also a trace amount of subarachnoid blood in this region in the fluid-attenuated inversion recovery sequences. Magnetic resonance angiogram (MRA) of the intracranial vasculature was normal (figure, B and C).

Question for consideration:

1. What is your most likely diagnosis?

© 2017 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Figure Imaging findings and photograph of the biopsy



(A) Cardiac MRI demonstrates patchy fibrosis of the basal and midinferior septum suggestive of myocarditis. The left ventricle was normal in size with severely reduced systolic function. Moderate pericardial effusion with systolic collapse of the right atrium and large right pleural effusion and moderate left pleural effusion are noted. (B) Brain MRI demonstrates an irregular area of restricted diffusion-weighted image in the posterior left temporo-occipital region indicating subacute ischemia. There was also a trace amount of subarachnoid blood in this region in the fluid-attenuated inversion recovery sequences. (C) Magnetic resonance angiogram of the intracranial vasculature is normal. (D) Transbronchial biopsy demonstrates non-necrotizing eosinophilic vasculitis affecting small vessels (×200).

GO TO SECTION 4

© 2017 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

SECTION 4

Tying the seemingly disparate symptoms together led to a final diagnosis of EGPA, known eponymously as Churg-Strauss syndrome, a rare systemic vasculitis affecting small and medium-sized vessels. The American College of Rheumatology established 6 criteria for the diagnosis of EGPA: (1) asthma; (2) >10% eosinophils on complete blood count; (3) mononeuropathy, mononeuropathy multiplex, or polyneuropathy; (4) migratory or transient pulmonary opacities detected radiographically; (5) paranasal sinus abnormalities; and (6) biopsy containing a blood vessel with extravascular eosinophilic accumulation. The presence of 4 of more of these criteria carries a sensitivity of 85% and a specificity of 99.7% for EGPA.[3]

An older clinically oriented diagnostic scheme referred to as the Lanham criteria listed 3 criteria as diagnostic for EGPA: (1) asthma; (2) peak peripheral eosinophilia >1,500 cells/μL; and (3) systemic vasculitis involving 2 or more extrapulmonary systems.[4]

Under either scheme, our patient can be definitively diagnosed with EGPA given her history of asthma, peripheral blood eosinophilia >10% and >1,500 cells/μL, systemic involvement of the brain and the heart, radiographically transient pulmonary opacities, and transbronchial biopsy showing small vessel non-necrotizing eosinophilic vasculitis.

Question for consideration:

1. What is the pathophysiology of neurologic involvement and how do you treat this patient?

DISCUSSION Our patient's condition illustrates many teaching points for the practicing neurologist, with initial consultation often occurring in the context of an unknown multiorgan system process possibly related to a vasculitis. These patients may have already been seen by other specialties without a unifying diagnosis being identified and the clinical question posed to the neurologist is often related to establish possible cause of underlying encephalopathy, polyneuropathy, or stroke. Thorough attention to the consultation question is often rewarded; beware of accidentally blinding yourself to the patient's true condition by failing to look at the patient's condition as a whole. Pertinent positives to remember when reviewing a new patient's history include asthma, renal insufficiency, cardiac involvement, and peripheral eosinophilia. If any of these are present and fit well with the diagnostic schemes, treatment should be initiated immediately.

Neurologic complications of EGPA are common, with peripheral nervous system involvement in 53%–78% of patients, and CNS involvement in 6%–39%.[5] Stroke in EGPA has been attributed to the release by the eosinophils of a major basic protein that damages the endothelium causing thrombosis and embolism, and eosinophil cationic protein that creates functioning nonselective pores in the neural membrane and potentiates a hypercoagulable state leading to thrombosis. Subacute progressive dementia and acute encephalopathy have been attributed to the diffuse toxin-mediated neuronal damage and direct infiltration of eosinophils into nervous tissue.[6] In cases of CNS involvement, demyelinating processes should be considered in the differential diagnosis because those can mimic small vessel vasculitis in MRI.[7]

The 5-factor score, a measure of vasculitic disease activity and prognosis prior to treatment initiation, is based on the presence or absence of 5 clinical factors: (1) age >65 years; (2) cardiac insufficiency; (3) renal insufficiency; (4) gastrointestinal involvement; and (5) lack of ear, nose, and throat manifestations.[8]

The mainstay of therapy of EGPA, regardless of the 5-factor score, consists of systemic glucocorticoids, usually oral prednisone 1 mg/kg daily. For acute multiorgan disease, consideration may be given to high-dose methylprednisolone (i.e., 1,000 mg daily) for several days prior to oral steroids. The vast majority of patients with EGPA achieve remission with steroid therapy alone. Often a slow 12- to 18-month glucocorticoid taper is required, with the majority of patients ultimately requiring long-term low-dose therapy.[9]

If the 5-factor score is 1 with mild organ involvement, azathioprine or methotrexate are usually added to the glucocorticoid regimen. If the 5-factor score is ≥1 with severe multiorgan involvement, monthly cyclophosphamide can be added. If the serum ANCA is positive, it is reasonable to add cyclophosphamide even with a 5-factor score of 0, as these patients frequently go on to develop renal insufficiency, peripheral neuropathy, and systemic vasculitis.[10]

For our patient, a burst of high-dose methylprednisolone, followed by an oral prednisone taper, quickly controlled her symptoms, with the eosinophil percentage dropping to <1% over a few days. Symptomatically, our patient seemed to require a dose of prednisone of 30 mg daily, with efforts to further taper limited by recurrent asthma attacks, dyspnea on exertion, and chest pain. With a 5-factor score of 2 for cardiac and renal insufficiency, cyclophosphamide induction has been planned in the near future to perhaps spare her continued relatively high-dose glucocorticoids. She had no recurrent ischemic events 1 month after hospital discharge. Her neurologic examination was unremarkable, and she has remained on aspirin 81 mg daily for secondary stroke prevention.

© 2017 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

AUTHOR CONTRIBUTIONS

Jorge G. Ortiz: evaluated the patient, acquisition of data, acquisition of images, manuscript design. Preston W. Douglas: evaluated the patient, acquisition of data, manuscript design. Chandler E. Gill: evaluated the patient, acquisition of data, manuscript design. Swati Mehrotra: performed the biopsy study, acquisition of biopsy photography, revision of the manuscript. José Biller: evaluated and diagnosed the patient, manuscript design, supervision, revision of drafts and final manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

J. Ortiz, P. Douglas, C. Gill, and S. Mehrotra report no disclosures relevant to the manuscript. J. Biller is chief editor of *Journal of Stroke and Cerebrovascular Disease*; field editor of *Frontiers in Neurology*; and an editorial board member of the Stroke Section of *Up-to-Date*. Go to Neurology.org for full disclosures.

REFERENCES

1. Biller J, Gruener G, Brazis P. DeMyer's the Neurologic Examination, 7th ed. New York: McGraw-Hill Education; 2017.
2. Greenberg SM, Vonsattel JP, Stakes JW, et al. The clinical spectrum of cerebral amyloid angiopathy: presentations without lobar hemorrhage. Neurology 1993;43:2073–2079.
3. 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;33:1094–1100.
4. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine 1984;63:65–81.
5. Wolf J, Bergner R, Mutallib S, Buggle F, Grau AJ. Neurologic complications of Churg-Strauss syndrome: a prospective monocentric study. Eur J Neurol 2010; 17:582–588.
6. Weaver DF, Heffernan LP, Purdy RA, Ing VW. Eosinophil-induced neurotoxicity: axonal neuropathy, cerebral infarction, and dementia. Neurology 1988;38:144–146.
7. Schneider R, Tsai JP, Munoz DG, Selchen DH. Eosinophilic CNS vasculitis can mimic demyelinating disease of the brain and spinal cord. Neurology 2015;84: 543–544.
8. Guillevin L, Pagnoux C, Seror R, et al. The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine 2011;90:19–27.
9. Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. Curr Opin Rheumatol 2007;19:25–32.
10. Sinico RA, Bottero P. Churg-Strauss angiitis. Best Pract Res Clin Rheumatol 2009;23:355–366.

MYSTERY CASE: A YOUNG WOMAN WITH TRANSIENT NEUROLOGIC SYMPTOMS

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group email sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media. We received 233 responses. The majority of respondents (61%) had just been in practice for 1–4 years; 56% were residents or fellows while 28% were faculty/board-certified physicians. A total of 85% resided outside the United States. A wide range of practice settings was represented.

When given initial information about this young woman's clinical presentation, including her preceding cardiorespiratory symptoms/signs and eosinophilia, and her episode of transient right visual field blurriness, and migrating right hemibody numbness, 67% of respondents correctly localized her transient deficit to the left parieto-occipital cortex. When asked to pick the top 3 differential diagnoses for this neurologic episode, the top choices were appropriately TIAs and their top mimics, namely migraine with aura and seizures (focal nonmotor).[1] In this case, the strange accompaniment of cardiorespiratory symptoms, history of atopy (asthma, allergic rhinitis), and eosinophilia should raise suspicions for more systemic etiologies associated with high eosinophils, and indeed the next 2 most popular choices were EGPA (39%)—formerly known as Churg-Strauss syndrome—and hypereosinophilic syndrome (HES, 20%); 12% also appropriately identified Loeffler endocarditis as a possibility.

Upon being presented the MRI/MRA images for this case, 59% of the respondents correctly identified the finding of left temporo-occipital ischemia (close enough to the clinically predicted localization) and 22% also identified the more subtle accompanying finding of left occipital subarachnoid hemorrhage. Only 16% explicitly identified the vasculature as being normal, this of course being a key consideration in the workup of a potential ischemic event. As this case illustrates, about a third of cases clinically consistent with TIAs have acute DWI lesions (+/− other lesions depending on etiology), which can be invaluable for diagnostic confirmation, setting aside the semantics of labeling these as TIAs/strokes.[2]

Upon being asked what top 3 investigations they would perform, 68% of respondents appropriately suggested testing for antibodies (ANA, ANCA, rheumatoid factor, or complement/immunoglobulins) potentially associated with a vasculitic etiology, given the confirmed vascular etiology for the patient's neurologic symptoms, on the background of more systemic features. The next 2 favored tests were TTE (46%) and lumbar puncture (34%); the former would help investigate potential cardiac contributors to this patient's TIA/stroke presentation (a further 12% also suggested cardiac MRI) while the latter would help

© 2017 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

assess for markers of CNS inflammation/infection. However, when thinking about establishing the diagnosis in this case, a tissue specimen would be especially helpful, and 11% recognized the value of obtaining a transbronchial biopsy. A total of 5% also recognized the importance of considering a nematode infection, which could cause eosinophilia with multiorgan symptoms.[3]

Finally, upon presenting the results of all the key investigations, including the findings of 31% eosinophils on bone marrow biopsy, pericardial effusion and bilateral pleural effusions on cardiac MRI, and dense eosinophilic infiltrate with necrotic debris on transbronchial biopsies, the majority of the respondents (53.6%) correctly picked EGPA as the most likely diagnosis. Another 24.9% picked HES. HES is characterized by persistent eosinophilia and organ involvement without a clear etiology, and can have similar cardiac and pulmonary manifestations as in EGPA, so the distinction can be tricky—but patients with HES usually do not have asthma or vasculitic complications, and the eosinophilia persists for >6 months.[4]

Aravind Ganesh, MD
Department of Clinical Neurosciences, University of Calgary, Canada; Nuffield Department of Clinical Neurosciences, University of Oxford, UK

REFERENCES

1. Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. Pract Neurol 2014;14:23–31.
2. Brazzelli M, Chappell FM, Miranda H, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. Ann Neurol 2014;75:67–76.
3. Walker MD, Zunt JR. Neuroparasitic infections: nematodes. Semin Neurol 2005;25:252–261.
4. Gioffredi A, Maritati F, Oliva E, Buzio C. Eosinophilic granulomatosis with polyangiitis: an overview. Front Immunol 2014;5:549.

© 2017 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Neurology®

Mystery Case: Diagnostic challenges in a young patient with hypereosinophilia

Jorge G. Ortiz, Preston W. Douglas, Chandler E. Gill, et al.

Neurology 2017;89;e159-e165
DOI 10.1212/WNL.0000000000004413

This information is current as of September 25, 2017

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/89/13/e159.full
References	This article cites 13 articles, 4 of which you can access for free at: http://n.neurology.org/content/89/13/e159.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Infarction** http://n.neurology.org/cgi/collection/infarction **Stroke in young adults** http://n.neurology.org/cgi/collection/stroke_in_young_adults
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology ® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

AMERICAN ACADEMY OF NEUROLOGY®