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CASE REPORT

Necrotizing eosinophilic granulomatous lymphadenitis with ring- and C-shaped granulomas—an underrecognized specific manifestation of nodal Churg-Strauss syndrome

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Abstract Nodal involvement as the main or prominent clinical manifestation of Churg-Strauss Syndrome (CSS) is uncommon but is being recognized with increasing frequency. Lymph node biopsies are only obtained in CSS cases in which the classic clinical and serologic manifestations of the disease are not clear, and thus the nodal biopsy becomes crucial for recognizing a disorder associated with severe morbidity and mortality. Unfortunately, lymph node pathologists are rarely confronted with this disease, and detailed descriptions of pathologic findings in nodal CSS are scant, with only one previous detailed report. We confirmed the specificity of the findings described in the previous report, and expanded the morphologic and immunophenotypic features of nodal CSS, including a possible pathogenetic role of IgG4. The diagnosis allowed successful treatment of symptoms that had plagued the patient for over 2 years and allowed the rapid recognition of a potentially fatal acute alveolar hemorrhage that occurred after the patient underwent an aortic valve replacement for bacterial endocarditis. Treatment with anti-interleukin-5 humanized monoclonal antibody mepolizumab allowed decreasing the risk of infection and poor healing associated with high-dose steroids and cyclophosphamide.

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Introduction

The diagnosis of Churg-Strauss Syndrome (CSS), or eosinophilic granulomatosis with polyangiitis (EGPA) as currently referred to, has traditionally relied on the presence of asthma, peripheral blood and tissue eosinophilia, and small vessel vasculitis, demonstrated by tissue biopsy. Additionally, the presence of necrotizing granulomas associated with eosinophilic abscesses in respiratory tract biopsies is considered pathognomonic of this disease [1]. The association of CSS/EGPA with perinuclear/anti-myeloperoxidase antineutrophil cytoplasmic antibodies (p-ANCA) and less commonly with cytoplasmic/anti-proteinase 3-ANCA (c-ANCA) in serum has greatly helped its recognition. Unfortunately 75% of the cases without renal involvement are ANCA-negative, in contrast to cases with necrotizing glomerulonephritis, which are usually positive [2]. Recently, the clinical and pathological manifestations of this disease have been recognized to be much more diverse [3]; it is unclear if these less common presentations are due to a modified disease course by commonly used steroids, variant forms of the disease, or early/subclinical phases incidentally identified during the work-up for unrelated disorders. We report a case of CSS/EGPA in which incidentally discovered lymphadenopathy was the dominant clinical finding. A diagnosis was established after an excisional lymph node biopsy showed characteristic pathologic changes, previously described in a single case report [4]. We describe results of immunomorphologic studies and discuss the

differential diagnosis and recently developed specific therapies.

Clinical history

A 63-year-old male underwent a preoperative chest X-ray for symptomatic cholelithiasis, which found a right lower lobe nodule. He was without respiratory symptoms, never smoked, and was employed mounting sheetrock. A chest computed tomography (CT) found numerous bilateral nodules, as well as mediastinal and axillary lymphadenopathy. The patient underwent needle followed by excisional axillary lymph node biopsies which revealed reactive hyperplasia with one C-shaped non-necrotizing granuloma. Microbiology and flow cytometry work-up were negative. Hematologic, rheumatologic, and infectious disease work-up was negative except for hypergammaglobulinemia (2.63 g/dL; range 0.6–1.7), increased C-reactive protein (7.2–19.8 mg/L; range 0–3), and erythrocyte sedimentation rate (41–48 mm/h; range 5–15). Over the next 24 months, he had multiple follow-up CT scans with numerous fleeting nodules, persistent lymphadenopathy, and had several dermatology consults for a chronic polymorphous skin rash for which repeated biopsies did not yield a specific diagnosis. He also developed intermittent symptomatic, lymphocytic pleural effusions with negative infectious, cytologic, and immunophenotypic work-up. He was referred to our pulmonary clinic where he described increasing fatigue, fevers, night sweats and wheezing while lying flat. A repeat excisional axillary lymph node biopsy showed changes diagnostic of CSS/EGPA. He was started on systemic corticosteroids, with rapid resolution of his symptoms, and improvement of his pulmonary nodules, lymphadenopathy, and pleural effusions. In retrospect, he endorsed respiratory allergies and sinus disease. Six months later, while tapering prednisone (3 mg/day), he presented with fever and chills and was found to have *Streptococcus agalactiae* endocarditis, presumed to have originated from a dental abscess. The patient underwent emergent aortic valve replacement for symptomatic insufficiency. A few days later, he developed diffuse alveolar hemorrhage requiring high-dose steroids. In an attempt to reduce risk for further infections and poor healing, prednisone was decreased to 5 mg daily and anti-interleukin-5 (anti-IL-5) therapy with mepolizumab was initiated. Six weeks post-surgery, he was asymptomatic and off prednisone, continuing mepolizumab injections monthly.

Material and methods

A 3-cm axillary lymph node was fixed in 10% buffered formalin and processed for histologic evaluation, which included hematoxylin & eosin (H&E), Gram, Warthin-Starry (W-S), Giemsa, Gomori-methenamine-silver (GMS) stain, acid-fast bacillus (AFB) and Verhoeff-Van Gieson (VVG) elastic stains. Immunohistochemical stains for CD1a (Cell Marque, Rocklin, CA, USA), CD3 (Thermo Fisher Scientific, Fremont, CA, USA), CD4 (Cell Marque, Rocklin, CA, USA), CD8 (Cell Marque, Rocklin, CA, USA), CD20 (Novacastra, Newcastle upon Tyne, UK), CD23 (Cell Marque, Rocklin, CA, USA), CD56 (Biocare Medical, Concord, CA, USA), CD68 (Dako, Glostrup, Denmark), CD138 (Cell Marque, Rocklin, CA, USA), PD1 (Cell Marque, Rocklin, CA, USA), TIA-1 (Biocare Medical, Concord, CA, USA), S-100 (Novacastra, Newcastle upon Tyne, UK), IgG4 (Cell Marque, Rocklin, CA, USA) were performed to characterize the nodal subpopulations. Immunostains for CD31 (Cell Marque, Rocklin, CA, USA), CD34 (Cell Marque, Rocklin, CA, USA) and smooth muscle actin (Cell Marque, Rocklin, CA, USA) were performed to evaluate the vasculature. Immunostains for herpes simplex virus (Cell Marque, Rocklin, CA, USA), cytomegalovirus (Cell Marque, Rocklin, CA, USA), toxoplasma (Cell Marque, Rocklin, CA, USA), and chromogenic in situ hybridization for Epstein-Barr virus (Novacastra, Newcastle upon Tyne, UK) were performed to exclude infections. Immunohistochemistry was performed on a Leica BOND-III automated stainer (Leica Biosystems, Melbourne, Australia) using EDTA buffer antigen retrieval protocols. Flow cytometry was performed on a six-color BD FACSCanto™ analyzer (BD Biosciences, San Jose, CA, USA). All procedures were performed in compliance with institutional guidelines (Veterans Health Administration handbook 1200.05).

Results

The touch imprints showed preponderance of small lymphocytes, frequent immunoblasts, a small proportion of eosinophils and plasma cells and epithelioid granulomas associated with venules. At low-power examination, the histologic sections revealed multifocal palisading granulomas, many of which were unusually “ring- or C-shaped”, surrounding areas of necrosis, or reactive lymphoid follicles, or areas of fibrosis (Fig. 1a). The remaining node showed mixed follicular and paracortical hyperplasia. The perinodal soft tissues had a prominent fibroinflammatory reaction (Fig. 1b).

The nodal granulomas had variable stages: early lesions showed non-confluent accumulation of histiocytes at the periphery of reactive germinal centers (Fig. 1c), intermediate lesions showed palisading granulomas surrounding foci of necrosis or reactive follicles (Fig. 1d, e), and a thin peripheral fibrous halo, late/burned-out lesions, showed fibrohistiocytic nodules surrounded by a thick hyalinized halo (Fig. 1f). High power examination of the necrotic areas revealed preponderance of eosinophils and prominent karyorrhectic debris (Fig.

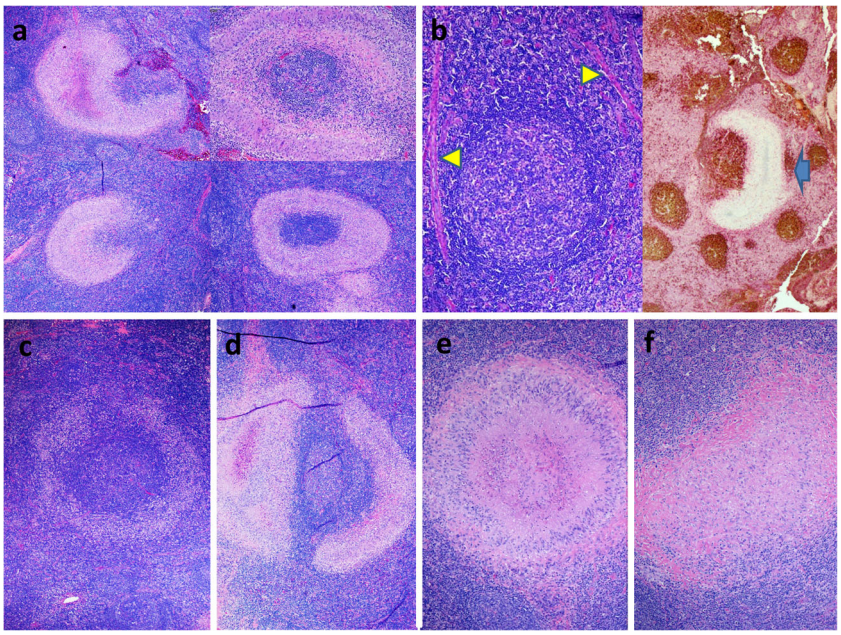

Fig. 1 Lymph node. **a.** C-shaped and ring-shaped granulomas surrounding areas of eosinophilic necrosis or reactive lymphoid follicles (H&E, ×10 objective). **b** *Left*: reactive follicle with prominent high-endothelial venules (*arrows heads*) resembling the distribution of the granulomas on the *left* (H&E, ×10 objective). *Right*: CD3 (*red*) and CD20 (*brown*) immunostains showing an unremarkable distribution of T and B subpopulations around a C-shaped granuloma [*arrow*] (2.5 objective). Early (**c**), active (**d**, **e**), and burned-out (**f**) granulomas (H&E, ×10 objective)

2a, b); less necrotic lesions showed eosinophils admixed with histiocytes containing abundant Charcot-Leyden crystals (Fig. 2c). Some of the reactive germinal centers contained numerous plasma cells (Fig. 2d) with a markedly increased IgG4/IgG ratio of 60% (Fig. 2e). The paracortical compartment was expanded with preponderance of small lymphocytes, numerous scattered immunoblasts and histiocytes, prominent high-endothelial venules (Fig. 2f), and variable number of eosinophils and plasma cells (Fig. 2g). The perinodal fibroinflammatory process had evidence of active and healed vasculitis (Fig. 3a, b), elongated serpiginous necrotizing granulomas (Fig. 3c) and areas resembling IgG4-related disease with storiform fibrosis admixed with chronic inflammation and numerous IgG4+ plasma cells (Fig. 3d). The most salient and characteristic finding of nodal CSS/EGPA was the ring- and C-shaped granulomas. A relationship between granulomas and existing vascular structures was not evident on H&E, VVG-stain, CD31, CD34, or SMA immunostains. The histiocytes within the granulomas showed preponderance of CD23−/CD31+/CD68+/CD1a−/S100− activated histiocytes and a small proportion of CD23−/CD31−/CD68+/CD1a+/S100+ Langerhans cells. The lymphocytes adjacent to the granulomas consisted of B cells in reactive germinal centers with normal CD4+/PD1+ follicular helper T cells, and paracortical T cells with a normal distribution of CD4+/PD1− and CD8/56+/− subpopulations. TIA1+ cytotoxic cells

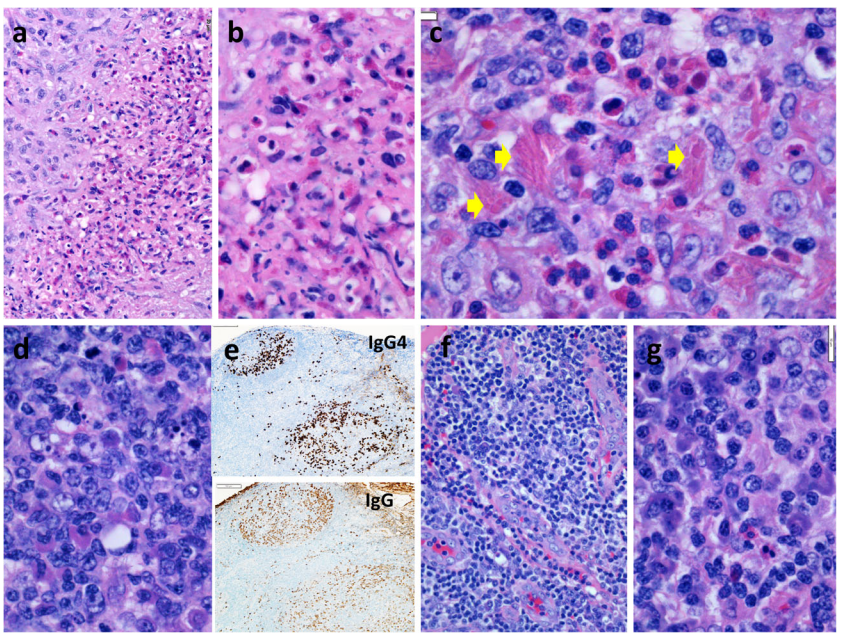

Fig. 2 Lymph node. **a.** Palisaded histiocytes surrounding "eosinophilic necrosis" (H&E, ×40 objective). **b.** Eosinophilic abscess and karyorrhectic debris (H&E, ×100 objective). **c.** Eosinophils admixed with histiocytes full of Charcot-Leyden crystals [*arrows*] (H&E, ×100 objective) **d.** Germinal center with increased plasma cells (H&E, ×100 objective). **e.** IgG4 and IgG immunostains: most of the plasma cells are IgG4+ (×5 objective). **f.** Expanded paracortex with prominent high-endothelial venules and scattered immunoblasts (H&E, ×40 objective). **g.** Paracortex with increased plasma cells and a few eosinophils (H&E, ×100 objective)

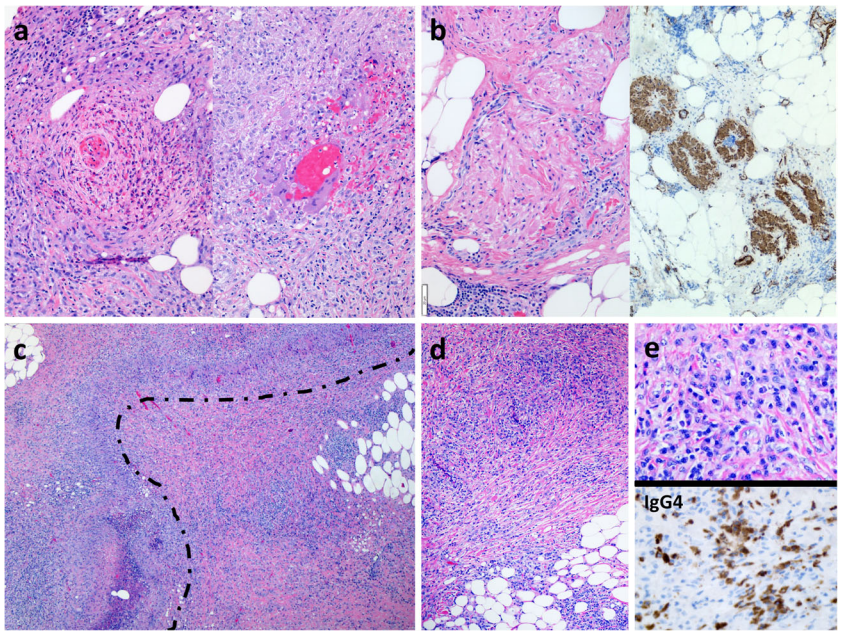

Fig. 3 Perinodal soft tissues. **a.** Active vasculitis: left eosinophil rich, right granulomatous (H&E, ×20). **b.** Healed vasculitis: obliterated muscular vessels (*left* H&E, ×20 objective; *right* smooth muscle actin ×10 objective). **c.** Long serpiginous necrotizing granuloma [*dotted line*] (H&E, ×5 objective). **d**, **e** Fibroinflammatory process with numerous IgG4+ plasma cells (H&E, *left* ×10 objective, *right* ×40 objective)

were not increased. Flow cytometry showed 77% T cells, 19% B cells, and 4% NK cells. Clonal B cell populations were not identified; the CD4 to CD8 were increased (CD4:CD8 = 10); T cell subpopulations did not show immunophenotypic aberrancies. Viral and microorganism stains were negative.

Discussion

The diagnosis of systemic vasculitis continues to be difficult because of the low frequency; protean and intermittent clinical course and common use of steroids affect their clinical and pathologic manifestations [5, 6]. The increased use of ANCA tests in the work-up of suspected vasculitis or unclear clinical syndromes has played a key role in their recognition. However, diagnosis of ANCA-negative CSS/EGPA, which comprises ~75% of cases without renal involvement [2], can be challenging, especially when presenting with non-classic symptoms as in our case. Tissue biopsy may be the only way of arriving to a diagnosis; but pathologists are rarely confronted with these disorders, and pathologic descriptions of organ involvement other than vasculitis or involvement of the respiratory tract are scarce. CSS/EGPA was originally described in an autopsy series in 1951 as the combination of asthma, blood and tissue eosinophilia, necrotizing vasculitis, and "allergic granulomas," which are palisaded granulomas surrounding eosinophilic abscesses, affecting the respiratory tract [7]. The 1990 American College of Rheumatology (ACR) [8] classification broadened the definition to include paranasal sinus abnormality, pulmonary infiltrates, neuropathy, and tissue eosinophilia without vasculitis as diagnostic criteria. The 2012 Chapel Hill Consensus Conference [5] definition maintained the ACR criteria and placed this disorder in the ANCA-associated small vessel vasculitides together with granulomatosis with polyangiitis (GPA/Wegener's). The pathologic criteria were refined by specifying that vasculitis may affect all intraparenchymal vessels from capillaries to medium-sized arteries and immune complexes must be few or absent. Skin manifestations are recognized to be varied and common, but are not defining criteria. While the sensitivity and specificity of the diagnosis increases with the number of positive criteria, it is also recognized that CSS/EGPA is a systemic disease and that any organ may be involved and that the occurrence and duration of each sign and symptom is highly variable. GPA also usually affects the respiratory tract and kidneys and may also develop systemic granulomatous and nongranulomatous extravascular inflammatory lesions, or present as limited forms confined to the respiratory tract or eye [6]; however, peripheral or tissue eosinophilia are not common features [5, 6]. While CSS is most commonly associated with ANCA specific for myeloperoxidase, GPA is most commonly associated with proteinase 3 ANCAs that correlate with perinuclear and cytoplasmic immunofluorescence patterns, respectively. Nodal involvement as the main or prominent clinical manifestation of CSS/EGPA has been recognized with increasing frequency since the early 2000's; this presentation has not been described in GPA [4, 9–12]. Most of these cases describe atypical clinical presentations, probably because in classic cases, a nodal biopsy would not be needed for diagnosis, and most have been reported in non-pathology journals, and thus the description of morphologic and immunophenotypic findings has been limited. The reported findings vary from simple lymphoid hyperplasia, plasma cell hyperplasia, hyperplasia with eosinophilia, and hyperplasia with "allergic granulomas," the pathognomonic finding of CSS/EGPA [9–12]. The only detailed immunomorphologic

description of nodal CSS/EGPA was done in a case report by Cualing H et al. [4] This group emphasized the presence of unusual ring- and C-shaped granulomas surrounding reactive follicles or eosinophilic abscesses in a reactive background. In our case, some granulomas consisted of fibrohistiocytic cells surrounded by thick hyalinized collagen consistent with healed/burned-out lesions. Prevasculitic, vasculitic, and postvasculitic phases of CSS/EGPA have been described [3]; the simultaneous presence of granulomas at different stages, and the fact that our patient had limited symptomatology, suggests intermittent episodes of disease activity of variable severity, more than well-defined phases of disease progression. Vasculitis was present in perinodal vessels, but not in the node; however, the shape and location of these "allergic granulomas" are reminiscent of the distribution of perifollicular high-endothelial venules (Fig. 1a, b upper right and upper left). Our case also had plasma cell hyperplasia with a markedly increased IgG4/IgG ratio. This has not been described previously in nodal cases; however, among classic autoimmune disorders, CSS/EGPA has been reported to have the highest IgG4 levels in serum, only comparable to IgG4-related diseases [13]. Interestingly, in the largest series of systemic IgG4-related lymphadenopathy, eosinophil infiltration and high serum IgE levels were present in most of their cases, suggesting that a hypersensitivity component is common to both disorders [14].

The differential diagnosis of nodal CSS/EGPA falls into three main groups: eosinophil and plasma cell-rich lymphadenitis, infectious suppurative granulomatous lymphadenitis, and granulomatous lymphomas with increased eosinophils. Table 1 summarizes the key diagnostic features of each group. The eosinophil and plasma cell-rich lymphadenitis group includes entities with patchy necrosis: Kimura's disease and drug-induced lymphadenopathy, and without necrosis: systemic IgG4-related lymphadenopathy. Similar to CSS/EGPA, this group is also frequently associated with systemic manifestations, peripheral eosinophilia, increased serum IgE levels, and hypergammaglobulinemia characteristic of systemic hypersensitivity reactions [14, 15]. In contrast to CSS/EGPA, granulomas are not a salient feature. The infectious suppurative granulomatous lymphadenitis group is usually caused by bacterial infections (cat-scratch disease, Bartonella, Yersinia, Tularemia, lymphogranuloma venereum) and only rarely by fungus [16]. The granulomas are the most salient feature, but neutrophils are the predominant cells within the areas of necrosis. Diagnosis is made based on specific exposures, microorganism stains (Gram, Giemsa, W-S, GMS, AFB), immunohistochemistry, and in selected cases, polymerase-chain-reaction studies. The granulomatous lymphomas with increased eosinophil group comprise mainly classical Hodgkin and T cell lymphomas. The diagnosis of Hodgkin lymphoma relies on the identification of Reed-Sternberg cells, which in cases with prominent granulomatous reactions can be difficult. Careful histologic assessment complemented by pertinent ancillary tests is the only way of

Table 1 Differential diagnosis of nodal CSS/EGPA

Lymphadenitis group	Specific entity	Key diagnostic features	Ancillary Studies
Eosinophil + plasma cell rich without granulomas	Kimura's disease	Usually affects head and neck nodes Patchy necrosis, prominent eosinophils, self-limited	Negative flow Negative microbiology
	Drug-induced lymphadenitis	Necrosis +/−; history of exposure to antiepileptics	Negative T and B gene rearrangement Increased serum IgE
	Systemic IgG4-related lymphadenopathy	Increased serum IgG4	Hypergammaglobulinemia
Suppurative necrotizing granulomas	Bacterial>>fungal lymphadenitis	Neutrophilic abscesses	Negative flow Positive microorganism stains
Granulomatous lymphomas with eosinophils	Classical Hodgkin lymphoma	Reed-Sternberg cells	Negative flow cytometry Classic CD15+/CD30+/CD45−/Pax5+ immunophenotype on tissue IHC
	T cell lymphoma (AILT, PTCL-NOS)	Variably prominent atypical lymphocytes in polymorphous background	Loss of Pan-T cell antigens by flow cytometry or tissue IHC Positive T cell gene rearrangement

AILT angioimmunoblastic T cell lymphoma, *PTCL-NOS* peripheral T cell lymphoma not otherwise specified, *IHC* immunohistochemistry

establishing this diagnosis. Among T cell lymphomas, angioimmunoblastic T cell lymphoma and peripheral T cell lymphoma not otherwise specified may present with systemic symptoms, peripheral eosinophilia, and hypergammaglobulinemia. They may also show many of the features described in CSS/EGPA: expansion of paracortex, vascular proliferation, polymorphous populations including eosinophils, histiocytes and plasma cells, and residual reactive follicles. Granulomatous reactions can be prominent in some cases (e.g., Lennert variants); however, palisading granulomas surrounding eosinophilic abscesses are not present. Immunophenotypic and T cell receptor gene rearrangement studies usually allow the identification of the abnormal T cell clone.

Our patient did not have a prior history of asthma, peripheral eosinophilia, or positive ANCA test. He did however have many of the less common features of CSS/EGPA: sinus symptoms, fleeting lung nodules, steroid-responsive skin rashes, lymphadenopathy, pleural effusions, fevers and night sweats, and diffuse alveolar hemorrhage, on histology evidence of necrotizing vasculitis and pathognomonic "allergic granulomas." His initial spirometry was at the lower limit of normal; however, after treatment, his measurements became supranormal. His response to corticosteroids and mepolizumab was excellent; the latter was used to prevent further complications. Only a few case reports/series [17–19] exist on the use of mepolizumab in patients with refractory or relapsing CSS/EGPA and the results of three ongoing placebo-controlled clinical trials [20–22] are yet to be published. The use of mepolizumab in the setting of an acute flare has not been previously reported, but its use seems intuitive given the proven efficacy of anti-IL-5 therapy in eosinophilic inflammatory processes.

In summary, we present a case of atypical CSS/EGPA diagnosed through lymph node biopsy. Recognizing the features of nodal CSS/EGPA has never been so relevant in light of increased recognition due to widespread use of imaging studies and effective therapies that can prevent, control, and modify the course of the disease.

Compliance with ethical standards The manuscript, or parts of it, have not been and will not be submitted elsewhere for publication. All authors have read and approved the manuscript. All authors acknowledge substantial participation and responsibility for this work. All procedures were performed in compliance with institutional guidelines (Veterans Health Administration handbook 1200.05).

Conflict of interest The authors declare that they have no conflict of interest.

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