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Lung involvement in hypereosinophilic syndromes

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Summary
Background: Hypereosinophilic syndromes (HES) are a heterogeneous group of conditions that are characterized by tissue-associated eosinophilic inflammation and peripheral eosinophilia. Although clinical and radiologic features associated with most forms of eosinophilic lung diseases are relatively well-described, there is little known regarding lung involvement in HES. The aims of the present study were to ascertain the frequency of pulmonary involvement in HES and define associated clinical and radiologic features.
Methods: We included all patients with HES seen over a 5-year period from 2004 to 2008 and examined their medical records and radiologic studies to obtain relevant data.
Results: There were 49 patients (25 males and 24 females) with a median age of 50 years (range, 12–88 years); 18 (37%) had a history of tobacco use. In 12 patients (24%), these pulmonary manifestations were attributable to parenchymal lung involvement with HES. Radiologic manifestations of pulmonary involvement varied but most commonly consisted of patchy ground-glass opacities and consolidation; one patient exhibited numerous pulmonary nodules. Thirteen patients (27%) had asthma including 6 with a new diagnosis of this disorder. Initial treatment usually consisted of corticosteroids but additional therapeutic agents were employed during the clinical course and included hydroxyurea, interferon-α, imatinib, and mepolizumab. Most patients with pulmonary involvement with HES improved and no deaths were observed.
Conclusion: One-quarter of HES patients manifested pulmonary involvement with variable radiologic findings. Asthma was more common in HES than previously reported. Most patients with pulmonary involvement in HES improve with currently available therapies.
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Abbreviations: CHIC2, cysteine-rich hydrophobic domain 2 locus; FEV_1, forced expiratory volume in 1 s; *FIP1L1*, Fip1-like 1 gene; FISH, fluorescent in situ hybridization; GGOs, ground-glass opacities; HES, hypereosinophilic syndromes; *PDRGFR*α, platelet-derived growth factor receptor α gene.

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Introduction

Hypereosinophilic syndromes (HES) are a heterogeneous group of conditions that are characterized by tissue-associated eosinophilic inflammation and peripheral eosinophilia.[1,2] The term, hypereosinophilic syndromes, was first coined in 1968 by Hardy and Anderson in describing three patients with diverse clinical presentations.[3] In 1975, Chusid and colleagues[4] proposed 3 criteria for diagnosing HES: (1) a persistent eosinophilia of $\geq 1.5 \times 10^9$/L for longer than 6 months, (2) a lack of evidence for parasitic, allergic or other known causes of eosinophilia, and (3) signs and symptoms of eosinophil-mediated organ dysfunction. More recently, Roufosse and colleagues[5] proposed that minimum duration (6 months) of eosinophilia criterion need not necessarily be fulfilled since some patients may require prompt treatment to mitigate end-organ damage. In addition, discovery of the myeloproliferative and T-cell lymphocytic variants of HES has led to classifying subtypes of hypereosinophilic syndromes.[2,5]

A spectrum of eosinophilic lung diseases is currently recognized and includes acute eosinophilic pneumonia, Löffler's syndrome (simple pulmonary eosinophilia), chronic eosinophilic pneumonia, Churg—Strauss syndrome, eosinophilic bronchitis, allergic bronchopulmonary aspergillosis, drug-induced eosinophilic lung disease, parasitic infections, and HES.[6—8] Although clinical and radiologic features associated with most of these eosinophilic lung diseases are relatively well-described, there is little known regarding lung involvement in HES, partly due to the rarity of this disorder.

In this study, we sought to ascertain the frequency of lung involvement in patients with HES and define associated clinical and radiologic features including the clinical course of these patients.

Methods

The study was undertaken at Mayo Clinic in Rochester, Minnesota, USA. A computer-assisted search was performed to identify all cases of HES diagnosed during a 5-year period from January 1, 2004 to December 31, 2008. HES was defined by the following criteria: (1) evidence of chronic illness lasting more than 6 months with blood eosinophilia of greater than 1500/μl ($>1.5 \times 10^9$/L) present on at least 2 occasions; (2) absence of other identifiable etiologies for eosinophilia including drugs, parasitic infection, malignancies, and allergic disease; (3) presence of signs and symptoms of organ dysfunction; (4) absence of recognized specific disease entities including Churg—Strauss vasculitis, acute or chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, and eosinophilic fasciitis.[1,4,5,8] Specifically, none of the patients exhibited anti-neutrophil cytoplasmic antibodies, histologic evidence of vasculitis, IgE or IgG antibody to *Aspergillus fumigatus*, or radiologic features of central bronchiectasis.

Medical records were reviewed and a total of 49 patients with HES were identified. Approval was obtained from the Mayo Foundation Institutional Review Board prior to beginning the study.

Data collection and analysis

Medical records of all patients confirmed as having HES were reviewed to extract data regarding demographics, clinical presentation, imaging and laboratory studies, comorbidities, diagnostic testing, treatment, and clinical course. In those patients with pulmonary manifestations, clinical or radiologic, determination was made as to whether the manifestation was directly related to pulmonary involvement with HES or not. Those patients designated as having pulmonary involvement with HES were required to have intrathoracic abnormality demonstrated on chest radiography or CT, no other plausible explanation for the intrathoracic finding, e.g., cardiac disease or infection, and one of the following: 1) evidence of eosinophilia on lung biopsy, bronchoalveolar lavage fluid, pleural fluid, or sputum, or 2) improvement of intrathoracic disease with treatment of HES.

Follow-up period was defined as the interval from the time of HES diagnosis to the date of the last available medical evaluation documented in the medical records.

Results

Demographic and clinical features

The study included 49 patients, including 25 men (51%) and 24 women (49%), with median age of 50 years (range, 12—88 years). Eighteen (37%) were previous or current tobacco users. The median duration of illness at presentation was 9 months (range, 1 month to 17 years). Four patients (8%) had myeloproliferative variant of HES with evidence of fusion of the Fip1-like 1 gene to the platelet-derived growth factor receptor α gene (*FIP1L1-PDRGFR*α) in 2 patients (all 49 patients were tested for *FIP1L1-PDRGFR*α fusion gene) and chronic eosinophilic leukemia in 2 other patients. Four patients (8%) were identified to have lymphocytic variant of HES with monoclonal T-cells (41 patients underwent lymphocyte phenotyping and 33 patients were tested for clonal T-cell receptor gene rearrangement). There were no patients with familial HES. The remaining 41 patients (84%) were diagnosed as idiopathic HES.

Thirty-one patients (63%) had one or more respiratory symptom including dyspnea (45%), cough (39%), and wheezing (24%) at initial presentation. Five patients (10%) manifested inspiratory crackles on auscultation of the lung. Skin rash had occurred in 19 patients (39%). Constitutional symptoms including fatigue, malaise, fever, night sweats, anorexia, weight loss, and/or myalgias were present in 27 patients (55%).

Chest radiography or CT revealed abnormal findings in 21 patients (43%) and included parenchymal infiltrates (37%), pleural effusion (14%), intrathoracic lymphadenopathy (12%), and pulmonary emboli (4%). The intrathoracic lymphadenopathy consisted of mildly enlarged mediastinal nodes with the exception of one patient who also had mildly enlarged hilar lymph nodes bilaterally. The pleural

Table 1 Demographic, clinical, and radiologic features of 12 patients with pulmonary involvement in HES.

Case no.	Age, year/sex	Presenting symptoms	Type of HES	CT findings	Pulmonary function	Lung biopsy	Treatment
1	57/M	Cough, weight loss	Idiopathic	Peripheral GGOs, bilateral pleural effusions	Mild obstruction	ND	Prednisone
2	88/M	Dyspnea, cough, rash	Idiopathic	Patchy GGOs and consolidation	Mild obstruction	Bronchoscopic — focal eosinophilic infiltrate	Prednisone
3	44/M	Cough, rash, fever, night sweats	Idiopathic	Patchy GGOs and consolidation, mediastinal lymphadenopathy, bilateral pleural effusions	Mild obstruction	ND	Prednisone, hydroxyurea, imatinib
4	48/F	Pruritus, arthralgias, weight loss, night sweats	T-cell lymphoproliferative variant	Patchy GGOs, bilateral pleural effusions	Normal	ND	Prednisone, interferon-α2b, hydroxyurea, imatinib
5	20/F	Dyspnea, headaches, myalgias, fatigue	Idiopathic	Focal consolidation	Normal	Surgical — eosinophilic pneumonia, bronchiolectasis	Prednisone, imatinib, mepolizumab
6	22/M	Dyspnea, chest pain, rash, arthralgias, fatigue, night sweats	Idiopathic	Patchy GGOs and consolidation, right pleural effusion	Mild obstruction	ND (Eosinophilic pleural effusion)	Prednisone, interferon-α2b, hydroxyurea
7	53/F	Dyspnea, cough, wheeze, diarrhea, weight loss	Idiopathic	Patchy GGOs and nodules	Severe obstruction, decreased diffusing capacity	Bronchoscopic — focal eosinophilic infiltrate	Prednisone, hydroxyurea, interferon-α2b
8	48/M	Dyspnea, myalgias, fever, nausea	Idiopathic	Patchy GGOs and consolidation, mediastinal lymphadenopathy	Moderate obstruction, decreased diffusing capacity	Bronchoscopic — respiratory bronchiolitis with eosinophils	Prednisone
9	68/F	Cough, dyspnea, rash	Idiopathic	Extensive GGOs and consolidation, left pleural effusion	ND	ND (Sputum eosinophilia)	Prednisone, interferon-α2b
10	68/F	Fatigue, dyspnea	Idiopathic	Peripheral GGOs	Normal	ND	Prednisone, interferon-α2b, hydroxyurea

11	45/F	Diarrhea, fatigue, night sweats	Idiopathic	Patchy GGOs	ND	ND	Prednisone, interferon-α2b, hydroxyurea, imatinib
12	32/F	Cough, rash	Idiopathic	Numerous nodules, mediastinal lymphadenopathy	ND	Surgical — angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma)	Prednisone, interferon-α2b

M = male, F = female, HES = hypereosinophilic syndrome, GGOs = ground-glass opacities, ND = not done.

effusion was small in all 7 patients with this finding and present bilaterally in 5 of these patients.

Pulmonary involvement in HES

Critical review of those patients with imaging abnormalities suggested that the intrathoracic findings represented direct pulmonary involvement with the eosinophilic infiltrative process in 12 of these patients, 2 of whom did not have respiratory symptoms or signs despite the presence of bilateral parenchymal infiltrates. In the remaining 9 patients, alternative causes of intrathoracic findings included cardiac disease with pulmonary congestion, pulmonary embolism, drug-induced lung disease (amiodarone), infection, aspiration, and chronic nonspecific fibrosis.

Details regarding the 12 patients (24% of total) with pulmonary involvement in HES are outlined in Table 1. Eight of these patients were never-smokers, one ex-smoker, and 3 were current smokers. Eosinophilic infiltrates were found in all 5 patients who underwent a lung biopsy procedure that included 2 video-assisted thoracoscopic surgical (VATS) biopsies and 3 bronchoscopic biopsies. One of the VATS biopsies (case #12) showed multiple well circumscribed nodules composed of a bland vascular proliferation admixed with numerous eosinophils and scattered lymphocytes (Fig. 1a and b). Eosinophils were also present in alveolar septa and in distal airspaces away from the nodules. These findings were most consistent with angiolymphoid hyperplasia (epithelioid hemangioma) of the lung. The other VATS biopsy (case #5) was not available for current review but reportedly showed histologic features of eosinophilic pneumonia, characterized by collections of eosinophils and macrophages in airspaces, and a mild interstitial inflammatory infiltrate. The transbronchial biopsies showed sparse and patchy infiltrates of eosinophils in the lamina propria of airway walls (Fig. 1c) and in alveolar septa (Fig. 1d and e). Eosinophilia was noted on pleural fluid examination (in the absence of prior pneumothorax or pleural procedure) in one additional patient and in a sputum sample in another patient (Fig. 1f). In the remaining 5 patients, radiologic abnormalities improved with treatment of the underlying HES, and there were no other likely causes for the intrathoracic findings.

Radiologic manifestations of pulmonary involvement in HES most commonly consisted of patchy ground-glass opacities (GGOs) and consolidation (Fig. 2). In one patient (case #9), these infiltrates were extensive and involved nearly half of the left lung (Fig. 3). In another patient (case #12), nodular opacities were noted diffusely throughout both the lungs (Fig. 4).

All 12 patients with pulmonary parenchymal involvement with HES were initially treated with corticosteroids. Other treatments included interferon-α2b, hydroxyurea, imatinib, and mepolizumab. The median follow-up was 14 months (range, 2—48 months) with no known deaths. Ten of these 12 patients experienced symptomatic and radiologic improvement on the treatment regimens outlined in Table 1. The remaining 2 patients were stable (case #4, 11) and in the process of modifying their treatment regimens.

Thirteen patients (27%) had asthma. There was a history of asthma in 7 additional patients but the diagnosis could not be

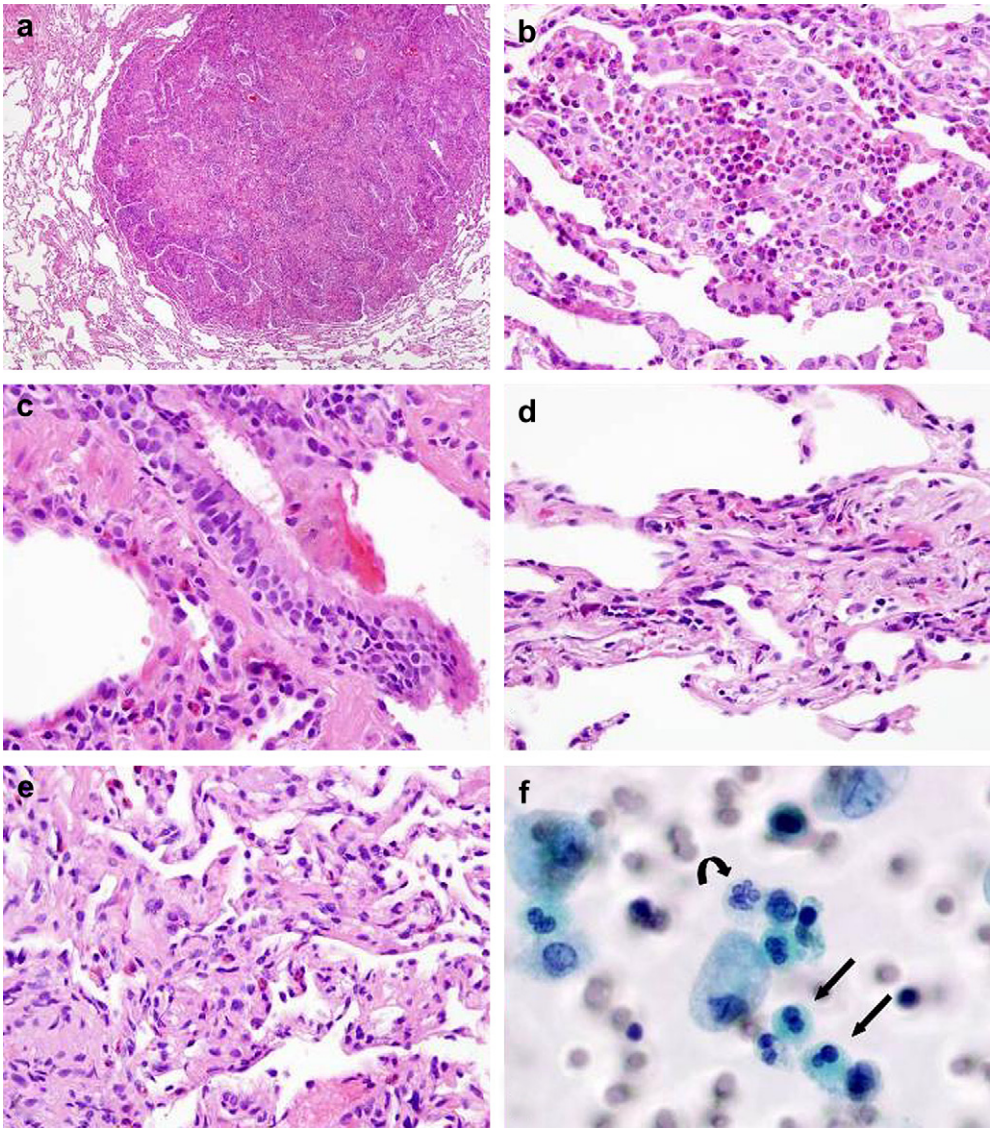

Figure 1 Morphologic findings in HES patients with lung involvement. a, b, VATS biopsy (case #12, Table 1) of angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma), forming nodules in the lung (low and high power). c—e, Transbronchial biopsies (case #7, Table 1) with scattered eosinophils in the subepithelial tissue of bronchioles (c) and in alveolar septa (d, e). f, Eosinophils in lavage specimens are recognized by their bilobed nucleus (straight arrows), compared with the polymorphonuclear appearance of neutrophils (curved arrow).

confirmed due to absence of documented reversible airflow obstruction. In 6 of 13 patients with confirmed asthma, asthma was diagnosed at the time of their presentation with HES and includes 2 of those described in Table 1 (case #7, 8). One of these patients (case #7) who presented with persistent dyspnea, cough, wheezing, diarrhea, abdominal pain, and 23-kg weight loss exhibited severe airflow obstruction (forced expiratory volume in 1 s [FEV_1] 0.45 L, 16% predicted) without acute response to inhaled bronchodilator and a severely decreased diffusing capacity (26% predicted) on pulmonary function testing. Prednisone treatment was initiated at 60 mg per day with gradual tapering of the dose. Five weeks later (on prednisone 40 mg per day), her FEV_1 had improved to 1.96 L (71% predicted) and the diffusing capacity was within normal range. Because her HES repeatedly worsened with tapering of the prednisone dose, hydroxyurea was added to her regimen which was later replaced with interferon-α2b therapy.

Discussion

Hypereosinophilic syndromes are characterized by peripheral eosinophilia and eosinophil-mediated organ dysfunction resulting in diverse clinical manifestations. Although lung involvement has been reported to occur in up to 63% of patients, associated clinical and radiologic features have not been well defined.[1,5,9] In our study, 67% of the patients had respiratory symptoms and/or radiologic abnormalities on chest imaging. Dyspnea and cough were most common symptoms as noted in previous studies. However, less than one-half of these patients (24% of all patients) had

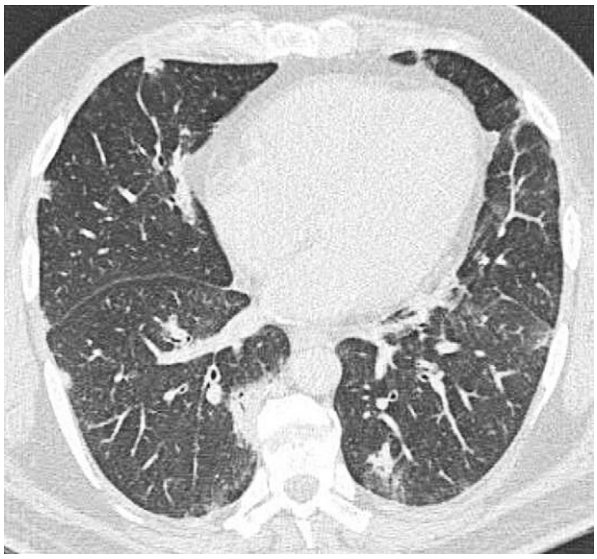

Figure 2 High-resolution CT scan of the chest of a 48-year-old man with HES (case #8, Table 1) demonstrating predominantly peripheral opacities of consolidative and ground-glass character in a patchy distribution.

evidence that the intrathoracic manifestations were directly attributable to HES, *i.e.*, eosinophilic infiltration of the lung. Other causes for respiratory manifestations included cardiac disease, pulmonary embolism, drugs, infection, aspiration, asthma, and other issues.

HES has previously been reported to be more common in men than women with a ratio of 9:1.[1,5,9] In our study, we noted a 1:1 ratio of men to women. This equal distribution between sexes was also noted in a recent study of mepolizumab therapy for HES patients who do not have the *FIP1L1-PDRGFR*α fusion gene.[10] Although HES related to *FIP1L1-PDRGFR*α fusion gene occurs almost exclusively in men, idiopathic HES and the lymphocytic variant of HES are equally distributed between the sexes. Most of our patients with HES including those with pulmonary involvement had idiopathic HES. The median age at diagnosis of 50 years in our study cohort is similar to that reported in previous studies.[4,9,10]

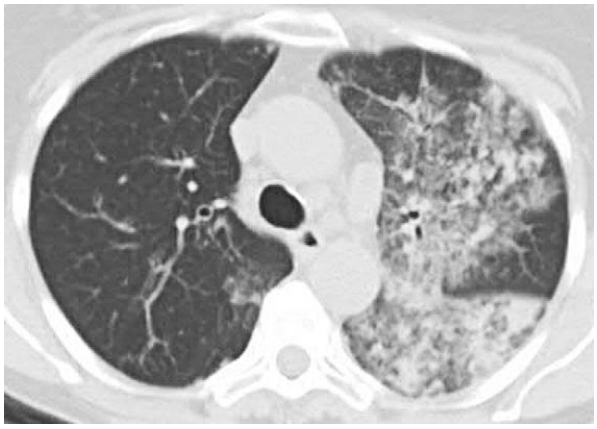

Figure 3 High-resolution CT scan of the chest of a 68-year-old woman (case #9, Table 1) demonstrating extensive consolidative and ground-glass opacities in the left lung with minimal involvement seen in the right lung.

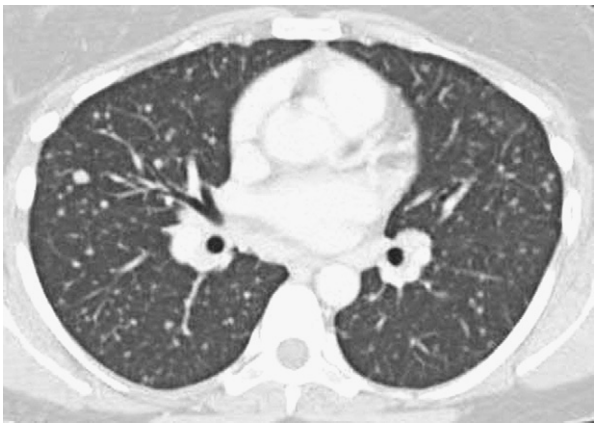

Figure 4 High-resolution CT scan of the chest of a 32-year-old woman (case #12, Table 1) demonstrating nodular opacities present diffusely throughout both lungs.

There was a relatively high frequency of asthma (27%) in our cohort of HES patients. In 6 of these patients asthma was diagnosed at the time of their presentation with HES. All 13 patients had reversible airflow obstruction or a positive methacholine challenge test. Our findings are contrary to those of Spry and colleagues[11,12] who reported that asthma was rare in HES patients. Our results suggest that asthma may be a manifestation of HES in some patients with this disorder. This association may be expected given the prominent role of eosinophils in the pathogenesis of asthma. In a patient with chronic asthma and persistent peripheral eosinophilia, the diagnosis of HES needs to be considered.

Pulmonary abnormalities on radiologic studies have been described in 14—28% of patients with HES and have consisted of nodules, ground-glass opacities, interlobular septal thickening, and pleural effusion.[13—15] In these previous studies, however, it was unclear whether the intrathoracic findings were directly attributable to eosinophilic infiltration or not. In our study, radiologic features most commonly consisted of a combination of ground-glass opacities and consolidation in a patchy distribution. In 2 of these patients, there was a peripheral distribution of these opacities, similar to that associated with chronic eosinophilic pneumonia, while in other patients the distribution was random. In patients with chronic eosinophilic pneumonia and extrapulmonary manifestations, alternative diagnosis of HES needs to be entertained. In 2 of our 12 patients, parenchymal involvement was detected by CT scanning in the absence of respiratory symptoms. In one patient, nodules were the predominant finding. This broad spectrum of radiologic findings is not surprising given the etiologic heterogeneity of HES that has been recognized through recent molecular diagnostic techniques.

Surgical lung biopsy is seldom performed in HES because pulmonary involvement may sometimes be inferred from the combination of clinical context and radiologic findings or established by bronchoalveolar lavage or transbronchial biopsy.[16] One of our patients underwent a surgical lung biopsy (case #12) which revealed angiolymphoid

hyperplasia with eosinophilia (epithelioid hemangioma) of the lung, a condition that most commonly affects the subcutaneous tissues and rarely involves the lung.[17] Recently reported association of this histologic finding with clonal
T-cell proliferations raises the possibility that this case may be an example of pulmonary involvement in lymphocytic variant of HES.[18] Clonality assessment was not performed in this particular patient. Increased number of eosinophils in the bronchoalveolar lavage fluid or eosinophilic infiltrate observed on the lung biopsy is not diagnostically specific but documents pulmonary involvement in patients with HES.

The majority of patients with HES have idiopathic HES, as noted in our study. For these patients, initial therapy is usually corticosteroids.[2,6] For those patients who do not respond adequately or tolerate corticosteroid therapy poorly, interferon-α, hydroxyurea, imatinib, and various chemotherapeutic agents have been used.[2,6,19] Rothenberg and colleagues[10] recently reported the use of mepolizumab (a humanized anti-interleukin-5 antibody) in patients with HES without the *FIP1L1-PDRGFRα* fusion gene and on prednisone therapy. Mepolizumab therapy was found to be an effective corticosteroid-sparing agent in these patients. The myeloproliferative variants of HES (including that associated with *FIP1L1-PDRGFRα* fusion gene) have been found to be responsive to treatment with the tyrosine kinase inhibitor, imatinib, which has become the first-line therapy for this variant of HES.[1,5] Hematopoietic stem cell transplantation is another option, particularly for those who are resistant to pharmacologic therapy.[20]

Due to its rarity, HES is a diagnosis that may be overlooked in the evaluation of patients with eosinophilic lung disease. For example, some patients with HES and pulmonary involvement may initially be diagnosed to have chronic eosinophilic pneumonia particularly in the absence of overt extrapulmonary manifestations. Furthermore, the boundary between HES and other eosinophilic lung diseases such as Churg—Strauss vasculitis can be blurred since these two disorders share some clinical manifestations such as asthma and peripheral neuropathy. Thus, judicious use of serologic studies, molecular testing for *FIP1L1-PDRGFRα* mutation, T-lymphocyte immunophenotyping, bone marrow examination, CT scanning of the chest, and tissue biopsy is needed along with appropriate clinical correlation to distinguish various forms of eosinophilic lung disease.

Limitations of this study are related to its retrospective nature and modest number of patients with this rare disorder. Clinical data were limited to those documented in the medical records. The diagnostic evaluation and treatment regimens employed were determined by individual physicians, usually hematologists and allergy/immunology specialists, involved in the care of these patients. Similarly, follow-up information, including subsequent radiologic studies, was limited to those contained in the medical records.

Nonetheless, our study provides new insights into the frequency and spectrum of pulmonary involvement in HES as well as the clinical course associated with this process. Although respiratory symptoms are relatively common in patients with HES, they may not necessarily be due to eosinophilic infiltration of the lung. CT scanning, bronchoscopy and, sometimes, surgical lung biopsy may be needed to clarify the cause of pulmonary manifestations in patients HES. Aside from parenchymal involvement, our data suggest that asthma may be a component of HES in some patients. Most patients with pulmonary involvement in HES respond favorably to currently available therapies.

Conclusion

One-quarter of HES patients manifested pulmonary involvement with variable radiologic findings but most commonly consist of patchy GGOs and consolidation. Asthma was more common in HES than previously reported. Most HES patients with pulmonary involvement experience improvement with currently available therapies.

Funding

None.

Disclosure

None.

Conflict of interest

None of the authors have any conflicts of interest to disclose.

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