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Title: On Patients, Diagnoses, Labels, and Truth, c 2009

Running Head: This is a case report of Pulmonary eosinophilia.

Word Count (text): 3047

Word Count (abstract): 109

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Competing interests: There are no conflicts of interest to disclose. One clinical department to which Robert Fowler belongs has participated in industry sponsored studies by Astra-Zeneca, Eli Lilly, Wyeth Pharmaceuticals, Novo Nordisk and Chiron corporation.

This study was not funded

Abstract

Eosinophilic disorders are rare and clinically challenging diagnoses. In part, the challenge comes from earlier classifications of eosinophilic diseases based on the site of eosinophilic infiltration, while others have focused on classifications based on the actual number of blood eosinophilis present. We describe a 54-year-old woman who frequented homeless shelters, had a history of asthma, and presented with dyspnea and eosinophilia. The differential diagnosis is broad and would include infectious etiologies, inflammatory conditions such as Churg-Strauss Syndrome, or hematological conditions such as hypereosinophilic syndrome. We describe the diagnostic challenges inherent in such a presentation, and also the changing landscape of disease labels in light of evolving genetic diagnostic ability.

A 54-year-old Caucasian woman presented to our emergency department after a three-week history of productive cough, shortness of breath, and general malaise. Four-weeks prior to admission she visited her family physician with otalgia and nasal fullness. She was prescribed a ten-day course of levofloxacin for sinusitis but developed increasing dyspnea on exertion, followed by fevers, chills, rigors, and intermittent night sweats.

A history of fever, productive cough, and pulmonary lung infiltrates is highly suggestive of community acquired pneumonia (CAP) [1]. Common bacterial causes of community-acquired pneumonia should have resolved with the prior appropriate antibiotic treatment [2]. In cases of a non-resolving pneumonia, other infectious etiologies such as tuberculosis, fungal infections, and parasitic infections should be considered. Resistant strains of typical community acquired pneumonia organisms such as *Pneumococcus,* and complications from primary pneumonia such as empyema or lung abscesses should be recognized.

Her family doctor saw her three days prior to her admission and prescribed clarithromycin (500 mg twice daily) for community acquired pneumonia. On the morning of her presentation to hospital, she was seen by her respirologist and found to be dyspneic at rest. A chest radiograph revealed bilateral, peripheral pulmonary infiltrates with central sparing. She was referred for further evaluation in search of a diagnosis.

Her prolonged course leads the clinician to suspect non-infectious etiologies associated with a non-resolving pneumonia including neoplastic conditions such as bronchogenic carcinoma, endobronchial carcinoid, and lymphoma, all of which may compromise the airway causing secondary obstructive pneumonia[3]. Inflammatory conditions such as systemic vasculitis, eosinophilic pneumonia, and bronchiolitis obliterans organizing pneumonia (BOOP) are possibilities in light of her findings on chest radiography[4]. Finally, drug-induced lung injury should be considered. It would be prudent to place the patient under respiratory precautions and obtain three sputum samples for *M. tuberculosis* in addition to bacterial cultures from blood, sputum, and urine. Legionella urine antigen determination should also be obtained. Further information regarding the patient's history should focus on past history, recent sick contacts, exposure to animals, travel history, and exposures to new drugs.

The patient resided in Toronto with her husband, and had no children or pets. Occupational history revealed that she was employed as a director of the Canadian National Shelter Program and traveled throughout the major cities of Canada inspecting shelters on a weekly basis. A tuberculin skin test performed 8 years before was negative. The patient denied all risk factors for Human Immunodeficiency Virus infection. She was a lifelong non-smoker and consumed five standard alcoholic beverages per week. She denied sick contacts, exposures to animals, or travel history.

The patient's occupational history and non-resolving symptoms make active tuberculosis a possibility. Because of overcrowding, poor ventilation, and large transient populations, the incidence of tuberculosis among the homeless in Toronto has been reported at 71 per 100,000[5]. This is ten times greater than the provincial rate and twenty times the incidence of TB in the general population of the United States[6]. The rates of transmission of tuberculosis to healthcare workers depend on geographical location and patient population; in the US, incidence of transmission to healthcare workers ranges between 1.0 and 14.6 per 100,000[6]. Typical symptoms of tuberculosis are insidious in nature, including fever, cough, night sweats, fatigue, and weight-loss for weeks to months prior to diagnosis[7]. Multi-drug-resistance in this population is high, largely based on poor compliance to the treatment regimen[8].

She had a history of allergic rhinitis, recurrent sinusitis, and asthma. Her asthma was treated with inhaled steroids, long and short-acting β_2 agonists, and a leukotriene receptor antagonist. She was started on montelukast eight months prior to her presentation and developed asthma exacerbations requiring systemic corticosteroids on two separate occasions six months prior to her admission.

The patient's history of recurrent sinusitis, asthma, and allergic rhinitis also raises the question of an underlying inflammatory lung disease such as Churg-Strauss syndrome and Wegener's Granulomatosis. Several reports in literature have linked leukotriene receptor antagonists to the development of a Churg-Strauss-like syndrome in the setting of oral steroid withdrawal. Case reports of both zafirlukast[9-11] and montelukast have supported this[11, 12]. The underlying mechanism is still unclear, but research suggests the syndrome is a pre-existing condition that is unmasked by the use of either montelukast or zafirlukast[13, 14]. In rare cases, some asthmatics receiving leukotriene receptor antagonists without prior steroid exposure and withdrawal have also developed Churg-Strauss syndrome[12].

Her medications on admission were clarithromycin, fluticasone, salbutamol, salmeterol, triamcinolone nasal spray, and montelukast. She had no known drug allergies, but was allergic to lactose, resulting in a previous anaphylactic reaction. Family history of pulmonary or rheumatological disease was negative.

Drug-induced lung injury can occur with antibiotics such as nitrofurantoin, ampicillin, and minocycline, as well as non-steroidal anti-inflammatory medications; but is uncommon with her current medications. Antibiotic-induced-eosinophilia is uncommon with clarithromycin[15], whereas levofloxacin can produce mild blood and pulmonary eosinophilia 2-3 weeks following exposure[16].

On examination, the patient appeared thin and in moderate respiratory distress. Her temperature was 38ºC, and she had a pulse rate of 104 beats per minute, blood pressure of 139/77 mm Hg, a respiratory rate of 34 per minute, and an oxygen saturation of 92 percent while breathing room air. Auscultation of the chest revealed decreased breath sounds throughout both lung fields with rales heard

predominantly in the left and right upper lobes. Examination of the precordium revealed normal heart sounds and the presence of a grade II/IV systolic ejection murmur heard best at the base of the heart. The remainder of the physical examination was normal.

The abnormal vital signs and chest findings on exam are still suspicious for pneumonia and would warrant further radiologically imaging to confirm the diagnosis[1]. Empirical treatment with broad-spectrum antibiotics should begin and the monteluklast discontinued pending further evaluation. Her occupational history and the insidious nature of her illness warrant further investigation for tuberculosis, however her history of asthma places Churg-Strauss syndrome high on the differential[17]. The absence of hemoptysis or bloody nasal discharge and oral ulcers on examination makes Wegener's Granunlomatosis less likely[18]. Routine blood work, urine analysis, and a chest radiograph should be performed.

Ceftriaxone and clarithromycin were initiated, and the montelukast was stopped. Blood work found the hemoglobin level was 14.6 mg per deciliter and the white blood cell count was 29,300 per cubic millimeter, with 37.8 percent neutrophils, 3 percent lymphocytes, 2 percent monocytes, 57 percent eosinophils, and no basophils (Figure 1). Arterial blood gas revealed a pH of 7.49, $PaCO_2$ of 35 mm Hg, PaO_2 57 mm Hg, and bicarbonate level of 27 mEq per liter. Hepatic enzymes and renal function were within normal limits. A chest radiograph revealed diffuse bilateral air space disease with upper lung predominance (Figure 2).

The fever and laboratory results suggest the presence of an inflammatory reaction. Although tuberculosis is still part of the differential diagnosis, it is often associated with either a normal blood count, or in prolonged courses, anemia, lymphopenia, and monocytosis rather than eosinophilia[1]. Bacterial pneumonia, though common, is unlikely given her ongoing symptoms and physical findings. The chest radiograph did not reveal a parapneumonic effusion, discrete rounded infiltrate, or cavitations, making the diagnosis of empyema or abscess very unlikely[19].

The patient's peripheral blood eosinophilia is striking. A pneumonic commonly memorized by American medical house staff is "NAACP", referring to the diagnoses: neoplasm, asthma, allergy, connective tissue disease, and parasitic infections; however, the full differential diagnosis of eosinophilia is much longer. Eosinophilia associated with lymphoma, asthma, and other connective tissue diseases tend to be less pronounced. Although she intermittently receives corticosteroids, a lack of travel history and risks for immune compromise makes parasitic infection less likely. The differential of dramatic eosinophilia in this patient with pulmonary symptoms includes the following main conditions: Churg-Strauss syndrome, drug reaction, and multi-organ hypereosinophilic syndrome. Tests for the presence of antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, and immunoglobulin titers should be sent.

Lactic acid dehydrogenease was elevated at 357 IU per liter. The erythrocyte sedimentation rate was 26 mm per hour. The C-reactive protein level was very high at 13.6 mg per deciliter. Rheumatoid factor, antinuclear antibody titer, anti-neutrophil cytoplasmic antibodies, and anti-glomerular basement membrane were negative. Immunoglobulin titers were normal aside from an elevated IgE at 1280 IU per liter.

I am now concerned about two main diagnoses. **Churg-Strauss syndrome** manifests with eosinophilia and pulmonary infiltrates[17]. The three components of the Churg-Strauss syndrome include allergic rhinitis and asthma, eosinophilic infiltration, and systemic small-vessel vasculitis[20]. **Hypereosinophilic syndromes** are disorders marked by sustained overproduction of blood eosinophils[21, 22]. The hypereosinophilic syndrome remains a clinical diagnosis with three defining features, including blood eosinophilia persistent for greater than six months, signs and symptoms of end-organ damage, and the exclusion of other etiologies. The clinical manifestation can mimic pneumonia, although cough tends to be non-productive in nature[23]. The lung opacities are diffuse and can be accompanied by small pleural effusions. The three main types of hypereosinophilic syndromes include a clonal variant, atypical myeloproliferative variant, and a T lymphocyte variant[21, 24, 25]

Despite antibiotic therapy, she remained febrile with a temperature of 39ºC, tachycardic at 110 beats per minute and tachypneic with a respiratory rate of 40 per minute. Her oxygen saturation was 92 per cent while breathing 35 percent oxygen. Cultures from blood, sputum, urine, and stool yielded no growth. Staining of three sputum specimens was negative for acid-fast bacilli. Urine for legionella antigen by Elisa test was negative. Computed tomographic scans of the chest revealed mild mediastinal lymphadenopathy with the right paratracheal nodes measuring 1.4 cm in diameter. There were small bilateral pleural effusions and extensive air space disease with scattered consolidation in all lobes and confluent consolidation in the upper lobes. There was no evidence of cavitation, loculation, or pleural irregularity (Figure 3)

Continued respiratory distress, eosinophilia, negative sputum staining for AFB, and failure to respond to antibiotic therapy make most infections unlikely. Eosinophilic lung diseases would rise to the top of the differential diagnosis. They represent a heterogeneous group of disorders that present with eosinophilia within the blood, bronchoalveolar-lavage (BAL) fluid, and lung parenchyma[26, 27]. The combination of pneumonitis, peripheral eosinophilia, and the patient's history of asthma warrants further consideration of Churg-Strauss syndrome and prompts the investigator to look for signs of systemic vasculitis elsewhere. Negative perinuclear anti-neutrophil cytoplasmic antibody serology and mild rise in ESR are consistent with the acute presentation of Churg-Strauss syndrome and should not exclude its diagnosis. The elevated IgE level supports a diagnosis of Churg-Strauss syndrome, but can be associated with hypereosinophilic syndrome as well[22, 28, 29].

On the third day of hospitalization she complained of increasing dyspnea and restrosternal chest heaviness at rest. The troponin-T was elevated at 0.94 ug per liter, the creatine phosphokinase was 290 IU per liter, and the MB fraction was 9 percent. Electrocardiogram revealed anterior ST segment and mild PR segment depression. Echocardiogram showed normal left ventricular size, ejection fraction of 50%, anterior wall hypokinesis, trace pericardial effusion, and no valvular abnormalities.

Chest pain, elevated cardiac enzymes, and ischemic changes on electrocardiogram should alert the clinician to an acute coronary syndrome or possibly pericarditis. However, the principle of Ockham's razor urges the clinician to look for a unifying diagnosis that encompasses a multisystem presentation. Cardiac involvement in Churg-Strauss syndrome can present as acute or constrictive pericarditis, heart failure, or myocardial ischemia[30]. In hypereosinophilic syndrome, eosinophilic myocarditis is caused by deposition of eosinophilic granules, and the production of IL-5 which leads to eosinophilic activation and myocardial injury[31]. Further evaluation with bronchoscopy and a bone marrow biopsy would be important to help differentiate these diagnoses.

Bronchoscopy revealed no discrete lesions, lavage fluid contained 92 percent eosinophils, 6 percent lymphocytes, 0 percent neutrophils, and 2 percent histiocytes. There were no malignant cells. Gram and AFB stain were negative. Transbronchial biopsy was deferred because no coagulation profile had been ordered. Bone marrow biopsy contained 45 to 55 percent eosinophilic hyperplasia. The marrow aspirate contained 45 to 55 percent eosinophils, with normal erythropoiesis and granulopoiesis. There was no evidence of nuclear atypia, granulomata, lymphoid aggregates, or metastatic cells (Figure 4). CT scan of the paranasal sinuses revealed minor mucosal thickening at the floor of the maxillary sinuses. The patient declined further procedures for pulmonary biopsy.

The profound eosinophilia within the lavage fluid and blood is consistent with both Churg-Strauss and hypereosinophilic syndrome. Radiographic imaging is non-specific and does not differentiate between these two etiologies. However, findings of sinus involvement are consistent with Churg-Strauss syndrome. Serological markers may be absent, especially since systemic vasculitis may not present until decades after the diagnosis of asthma and pulmonary eosinophilia[20]. Bronchial biopsies revealing parenchymal eosinophilic infiltration occur in both hypereosinophilic syndrome and Churg-Strauss syndrome; however, the former is characterized by infiltration of eosinophilic masses, while the latter presents with eosinophilic infiltrate, angiitis, and extravascular necrotizing granuloma[32]. Although lung biopsy would be helpful, it would have been inappropriate to perform without knowledge of the bleeding risk to the patient. Although bone marrow involvement is common with hypereosinophilic syndrome[22], there has been a case of bone marrow eosinophilic hyperplasia in the setting of Churg-Strauss syndrome[33]. At this time, given her progressive hypoxemia and respiratory distress, corticosteroid therapy should be initiated. Further specific investigations for hypereosinophilic syndrome including cytogenetic testing for the tyrosine kinase FIP1L1-PDGFR alpha, and interleukin-5 levels would be important.

Antibiotics were discontinued and the patient was treated with prednisolone, 50 mg once daily. Her cough, fever, and dyspnea resolved over the next 5 days. Her white blood cell count and differential normalized. Repeat chest radiograph prior to discharge revealed improvement in the bilateral lung opacities and a repeat ECG was negative for ischemia. Our patient's respirologist believes her to have Churg-Strauss syndrome while her hematologist believes this is likely a variant hypereosinophilic syndrome. Both agree that a tapering dose of steroids is the most prudent current therapy.

Despite the diagnostic dilemma, the management of non-infectious pulmonary eosinophilia due to Churg-Strauss or hypereosinophilic syndrome first includes systemic corticosteroids. Other treatments for Churg-Strauss syndrome that are non-responsive to corticosteroids include immunosuppressive agents such as cyclophosphamide, azathioprine, and intravenous immunoglobulin[34, 35]. In hypereosinophilic syndrome, chemotherapeutic agents such as hydroxyurea, chlorambucil, vincristine, and etoposide can be used as long-term regimens in steroid unresponsive [22, 36]. For a subset of hypereosinophilic syndrome patients with a myeloproliferative-like disorder that results in constitutively activated tyrosine kinases, recent evidence supports the use of imatinib, a tyrosine kinase inhibitor[24]. In several case series, clinical, hematological, and molecular remission has been documented following the use of imatinib[24, 37, 38]. Interferon alfa and anti-interleukin-5 antibodies have also shown promise; the mechanism likely involves inhibition of eosinophilic proliferation[39-41].

The patient was discharged home on the prednisolone with instructions to slowly taper her dose to 20 mg. An outpatient echocardiogram demonstrated resolution of wall motion abnormalities. Cytogenetic studies were negative for F1P1L1-PDGFR alpha mutation and interleukin-5 levels were negative. At one year from her presentation, she remains well on low dose oral prednisone.

1COMMENTARY

This patient presented with signs and symptoms of a common medical condition – community acquired pneumonia. Her failure to respond to appropriate treatment was the initial clinical clue that this diagnosis was not correct. Her occupational history and non-resolving symptoms were concerning for tuberculosis, however the history of asthma, use of leukotriene antagonists, and impressive peripheral eosinophilia was suspicious for an underlying inflammatory condition.

Churg-Strauss syndrome is a rare and clinically challenging diagnosis. In part, the challenge comes from its similarities with other common diseases such as asthma. Accordingly, the natural history of Churg-Strauss syndrome includes a long prodromal period[20, 42]. However, case series have suggested that Churg-Strauss syndrome, though rare, should be easily recognized. Solans et al reported that in a series of 32 patients diagnosed with Churg-Strauss syndrome, all presented with asthma and hypereosinophilia, 53 percent had infiltrates on chest radiograph at initial presentation, and extravascular granulomas were rarely found on biopsy[43]. Similarly in a case series of 96 patients followed by Guillevain et al, 97.9% had asthma at presentation and 37.5% had infiltrates on chest radiograph[20].

According to the American College of Rheumatology, four of six criteria must be met to establish the diagnosis of Churg-Strauss syndrome: asthma, hypereosinophilia greater than 10 percent, mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils[17]. Antineutrophil cytoplasmic antibodies are present in many systemic vasculitides and therefore important but not specific to the diagnosis of Churg-Strauss syndrome. The negative ANCA serology in this case does not dissuade the clinician from the diagnosis; instead, it highlights the phenotypic variations between ANCA-positive and ANCA-negative Churg-Strauss syndrome[44]. The seropositive syndrome is frequently a more fulminant, vasculitic process presenting with renal involvement and peripheral neuropathy[44] whereas the seronegative syndrome presents with isolated pulmonary symptoms, fever, and cardiac involvement[44, 45]. Eosinophilic hyperplasia within the bone marrow is common in hypereosinophilic syndrome, but has been found in rare cases of Churg-Strauss [33]. Although tissue pathology is considered the gold standard for extravascular manifestations, it is obtained in a minority of cases[42]. This patient's clinical history, previous exposure to leukotriene receptor antagonists, and negative cytogenetic analysis supports the diagnosis of Churg-Strauss *syndrome* and makes the diagnosis of currently appreciated hypereosinophilic *syndromes* less likely.

What should clinician's call this patient's "disease"? Our classical training pushes our differential diagnosis towards Churg-Strauss syndrome, in part due to the prominence of pulmonary involvement. However, the spectrum of organ involvement challenges our allegiance to a specialty or organ-focused classification of illness. Traditional clinical categories of disease are in flux, especially so for conditions caused through genetic predisposition or alteration. Churg-Strauss syndrome or hypereosinophilic syndrome are

arbitrary labels we have applied to combine clinical and pathological presentations. The increasing appreciation of underlying genetic abnormalities has sparked a revolution in the diagnoses of many blood dyscrasias. Churg-Strauss syndrome is not merely a *pulmonary* disease or a *rheumatological* diagnosis, but nearly certainly, an expression of a more proximate abnormality; as much as pulmonary edema is not a diagnosis, but a manifestation of congestive heart failure, itself with many causes. For now, our patient will carry the label of Churg-Strauss syndrome and dutifully report it as part of subsequent history taking by our colleagues. That traditional immune suppressing therapy has helped will reinforce our notion of how Churg-Strauss syndrome should behave; however, we do not yet know the real cause for her illness, or the optimal level of labeling to apply.

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Figure headings

Figure 1: Peripheral blood film and eosinophilia

Figure 2: Chest radiograph (anterior-posterior view)

Figure 3: Computed tomogram of the chest at the level of the carina

Figure 4: Bone marrow biopsy and eosinophilia

Figure 1: Peripheral blood film and eosinophilia

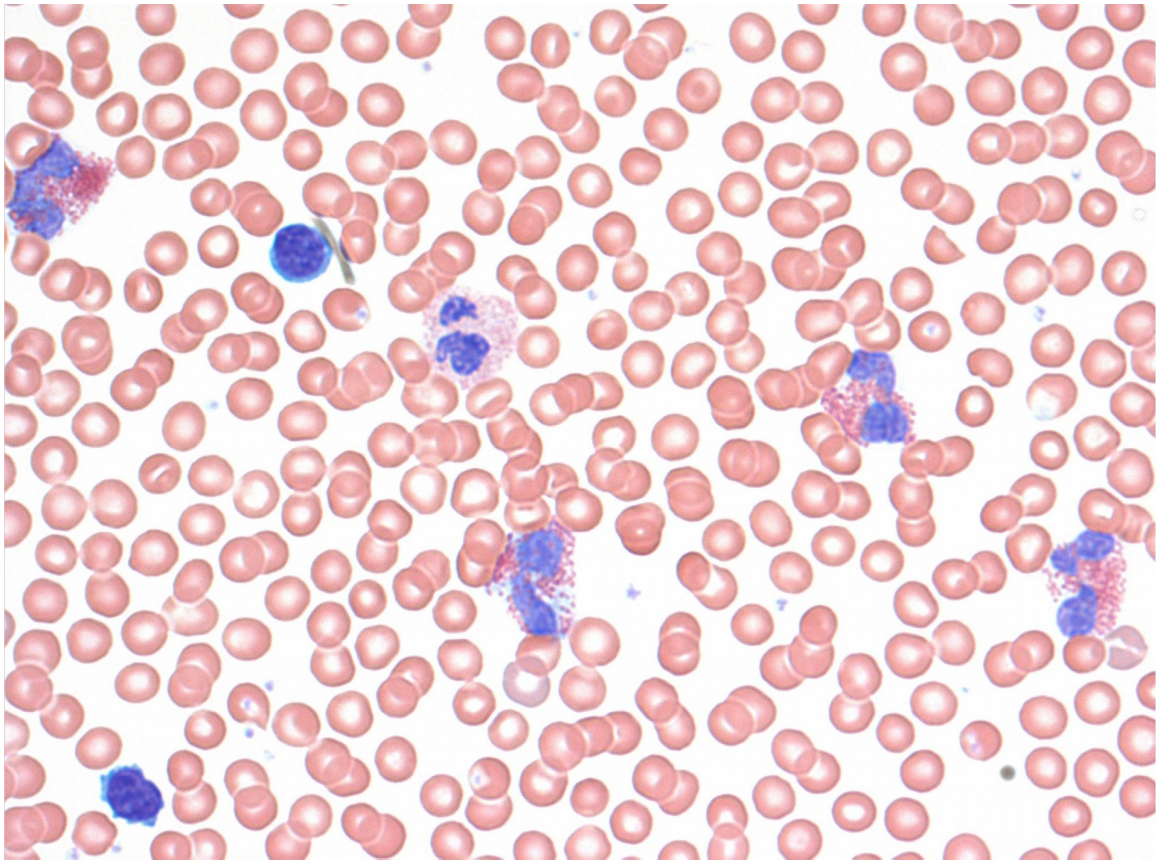

Figure 2: Chest radiograph (anterior-posterior view)

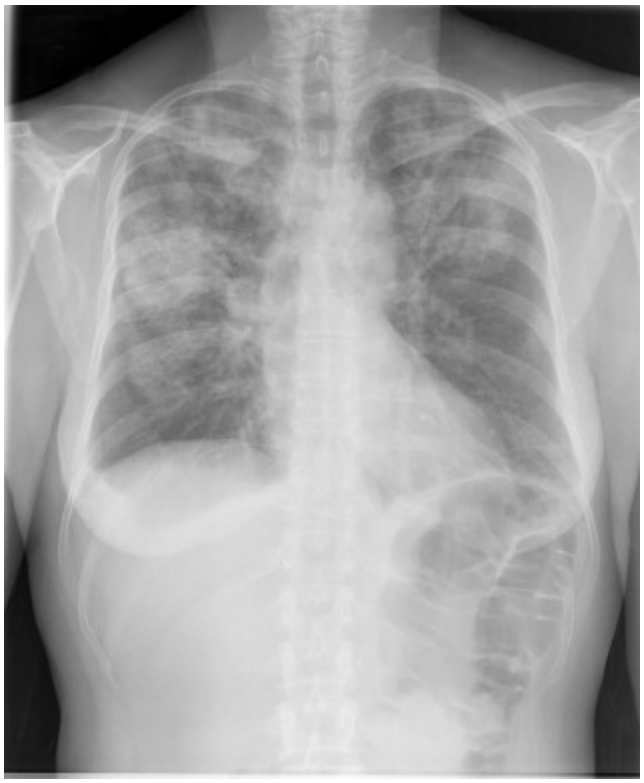

Figure 3: Computed tomogram of the chest at the level of the carina

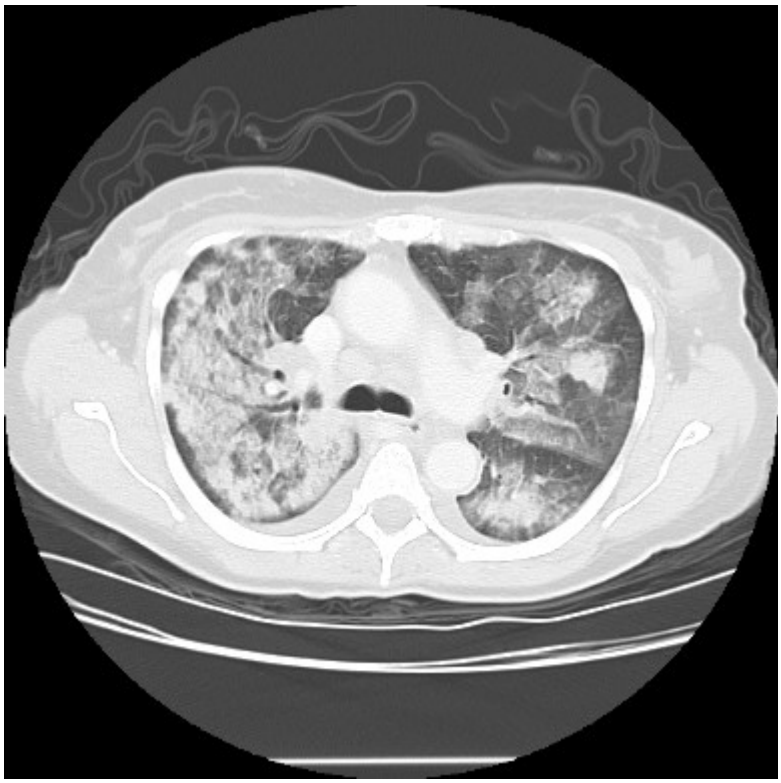

Figure 4: Bone marrow biopsy with eosinophilia