Co-existence of Crohn's disease, sarcoidosis and malignant lymphomas

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Crohn's disease and sarcoidosis, two systemic granulomatous disorders, on rare occasions co-exist.

Case report

In 1997, at the age of 42 years, an African-American woman was diagnosed with Crohn's disease. She was appropriately treated with prednisone and mercaptopurine. In early 2007, she had a normal colonoscopy. In the latter part of 2007, she developed dyspnoea, retrosternal discomfort and diffuse joint pains, mainly on the left side. Other associated symptoms were dry cough, hoarseness of the voice, diarrhoea and athralgia, and she was initiated on prednisone 40 mg for a suspected Crohn's flare. Further evaluation in early August 2008 revealed bilateral hilar adenopathy, diffuse nodular opacities on a chest X-ray film. Admission physical exam revealed the patient to be afebrile, normotensive and comfortable with 95% O_2 saturation on room air, with a regular, unlabored respiratory rate of 18. On palpation, patient was tender on the left superior-axillary chest wall, with all other systems unremarkable on assessment. Admission labs are noted in Table 1. In addition, CRP was 2.1 mg/dL.

High-resolution CT identified a 5×4.9 cm soft tissue mass in the right hilar region, soft tissue consolidation within the left upper lobe measuring 10×6.2 mm, nodular opacities, and enlarged parenchymal nodules. Pulmonary function tests at baseline are noted in Table 1. Prednisone was weaned from 40 mg to 15 mg for severe depressive symptoms.

During the latter part of August, the patient underwent bronchoscopy and biopsy of the right hilar lesion with negative cultures and was discharged home with a decrease in her ranitidine dose, the addition of lansoprazole every morning, and an increase in prednisone from 15 mg q day to 40 mg q day.

Four months later, in December, the patient was seen on follow-up for continued complaints of progressively worsening cough and wheezing and was admitted. Pulmonary function tests are noted in Table 2 for comparison. Chest CT reported an increased obstruction of the right middle lobe; mercaptopurine was increased to 125 mg. She underwent a bronchoscopy with washing, removal of granulosis tissue of right lower lobes, and an initial balloon dilation of the right main bronchus was performed.

One week later, the patient re-presented for persistently increasing wheezing episodes which led to a repeat dilatation on an outpatient basis.

Postprocedure follow-up on 2 January 2009 by CT revealed increased soft tissue in the right hilar region and persistent obstruction of the right middle lobe bronchi. Abdominal CT revealed an ill-defined hypoattenuating lesion within the right hepatic lobe and a small rounded density within the gallbladder. Electrolytes and LFTs were normal; an elevated ferritin of 1569 was observed.

Bone marrow biopsy pathology identified Epstein-Barr virus (EBV) positive large B cell lymphoproliferative disorder, large atypical cells with positivity for BOB.1, Oct-2, CD79A, and EBER, and CD20 negative with hypocellular marrow with normal cytogenetics and no evidence of clonal lymphoproliferative disorder. The patient was then referred to haematology/oncology; meanwhile, her clinical condition worsened, she developed 'continuous' coughing, nausea, vomiting, intermittent sweats, shortness of breath, weight loss and fatigue. Physical examination revealed unlabored respirations with room air O_2 saturation of 93% and 87% on exertion. An

Table 1
Complete blood counts and coagulabilities 2008 and 2009

	26 August 2008	*5 December 2008*	*21 January 2009*	*28 January 2009*	*18 March 2009*	*October 2009*
WBC (K/uL)	4.65	7.18	0.32	10.34	3.10	4.34
Hgb (g/dL)	12.4	9.7	9.5	9.2	10.7	13.5
Hct (%)	36.4	28.1	27.9	28.1	32.3	40
Platelets (K/uL)	500	891	291	578	576	533
PT (s)	14.0	14.2	Not reported	Not reported	Not reported	Not reported
PTT (s)	34	33	Not reported	Not reported	Not reported	Not reported

echocardiogram was performed and evaluated as normal, with an estimated ejection fraction of 61% and no valvular anomalies. Home oxygen was initiated; methotrexate and 6-MP were stopped.

At haematology/oncology follow-up in mid-January 2008, the patient's respiratory rate was unlaboured at 18, with 94% saturation on 1.5L NC. Physical assessment aberrations included bilateral wheezing. CHOP (cyclophosphamide/hydroxydaunorubicin/oncovin/prednisone) chemotherapy, clarithromycin 500 mg bid, and Neulasta are initiated following negative HIV testing and EBV polymerase chain reaction testing. EBV DNA detected at 4.7 log copies/mL. AFB culture demonstrated *Mycobacterium gordonae*.

Chest X-ray demonstrated an increasing mass-like opacification in the right middle lobe with surrounding perihilar opacities extending to the right lower lobe. An additional bronchoscopy was performed for persistent cough and right-sided chest pain. Chemotherapy-induced neutropenia is resolved with Neulasta administration, as seen in Table 2.

Table 2
Pulmonary function tests October and December 2008

	20 October 2008	*December 2008*
FVC	3.33 (predicted 88%)	3.12
FEV1	2.54 (predicted 86%)	1.95
DLCO	24.32%	21.73
6-minute walk test	1989 feet, nausea, no dyspnoea	1718 feet

By mid-February, subsequent HRCT study revealed a new narrowing of the right lower lobe bronchus with new central consolidation and clustered small centrilobular and tree-in-bud opacities, as well as a new, small right pleural effusion. Due to airway narrowing, the patient underwent a third outpatient bronchial dilation and continued with Neulasta and CHOP. Prednisone is decreased to 7.5 mg q day in between each 21-day cycle of CHOP.

In March, the patient reported worsening shortness of breath, coughing and chest pain, and underwent her fourth bronchial dilation in three months. Postprocedure vitals demonstrated improved saturation on room air at 96%. Neutropenia is now resolved, normal electrolytes and LFTs were evaluated and no changes on X-ray were observed.

An HRCT on 6 April is interpreted with minimal reduction of right hilar mass and adenopathy, hepatic lobe lesion is now absent on abdominal/pelvic CT. During physical examination, the patient complained of 'airway fullness'. Wheezes are noted on auscultation in the right mid-hemi thorax. A flexible bronchoscopy and repeat tracheal dilation is performed. CHOP #5 and #6 are tolerated with an additional prednisone decrease to 5 mg every other day.

In May, a repeat PET CT from skull base to mid-thigh was performed with an increase in right hilar adenopathy and soft tissue mass of 5.2 × 1.8 cm, with consolidative densities suspicious for a lymphomatous spread, post-obstructive infiltrates, hyper metabolic lymph nodes in the porta hepatitis and peripancreatic distributions, with

multiple sites of hypermetabolism within the bones, including the left hilum.

Following CHOP #6, vitals remained stable, breath sounds were now clear to auscultation, and the patient was saturating 96% on room air. CBC, BMP and LFTs were all normal; CRP was reduced to 0.3. A bone marrow biopsy and bronchoscopy with biopsy were performed. Prednisone was discontinued.

Bone marrow biopsy shows normocellular marrow at 50% with trilineage hematopoiesis with non-caseating granulomas. Peripheral blood smear showed mild macrocytic normochromic anemia, neutrophils with a left shift and toxic changes, absolute lymphopenia and mild thrombocytosis.

On 15 July 2009, the patient presented for a follow-up with additional complaints of wheezing and dyspnoea and received an additional bronchoscopy and sixth bronchial dilation, as well as thoracic surgery evaluation for possible resection due to the frequency of her airway dilations.

Thoracic surgery evaluation in August led to a right lung resection/middle lobe pneumonectomy secondary to closure of the right middle and lower lobe.

Follow-up by haematology/oncology addressed the patient's reports of shortness of breath unresolved by surgical intervention, with the additional complaint of a weight loss of 12 lbs. CBC and electrolytes were normal. PET CT of skull base to mid-thigh in October revealed significant progression of sites of disease within the skeleton, left lung, right pleural surface, and lymph nodes of the neck, axilla, and mediastinum, left hilum, perioportal, retroperitoneal, iliac, and inguinal regions. A left supraclavicular lymph node is measured at 8 mm, with an approximate growth of 3 mm from previous scans. Operative pathology showed benign lung parenchyma involvement by non-caseating granulomatous inflammation. No morphologic evidence of lymphoma. Mycobacterial and fungal stains were negative.

On 30 November 2009, the patient was evaluated for possible Remicade use.

Discussion

Sarcoidosis and Crohn's

The incidence of both sarcoidosis and Crohn's disease co-existing in a patient has been suggested as early as 1947[1] with very few definite cases reported in the literature. Fries *et al.*[2] produced two cases of both inflammatory bowel disease and sarcoidosis, but were unable to identify a link between the two conditions. These granulomatous disorders are often reported as 'mimicking' one another, with up to 10% of patients affected by sarcoidosis to have alimentary tract involvement[3] and approximately 40–50% of patients with inflammatory bowel disease[4,5] to demonstrate respiratory symptoms. Published hypotheses suggest a genetic link, with CARD15, a known mutation that contributes to Crohn's having no relation to sarcoidosis incidence[6] in one study with some familial incidence of both disorders identified by Willoughby *et al.*[7] and Gronhagen-Riska *et al.*,[8] whereas the autoimmune response of both diagnoses may include a common pathogenesis and immune response. The National Heart, Lung, and Blood Institute utilized Crohn's disease as a model for the study of sarcoidosis in 2004, identifying three key similarities between the two: (a) both are chronic granulomatous inflammatory processes that (b) result in helper T cell type 1 inflammation as a primary immune response and (c) may result from both environmental and genetic factors that remain unknown at this time.[9] We recognize the rarity of our patient presenting with both disease processes simultaneously.

Lymphoma and Crohn's

In 2009, *The Lancet*[10] reported results from the French CESAME group, indicating a hazard ratio for LPD of 5.28 for patients with inflammatory bowel disease (IBD) receiving thiopurines for immunosupression, with additional risk for increased age, male sex and chronic histories of IBD. Patients primarily presented with non-Hodgkin lymphomas associated with EBV. The Pyramid and ENCORE registries are currently evaluating the risk of developing lymphoma with anti-TNF medications without thiopurine use.

Smith *et al.*[11] published a review article of association of thiopurines and its use in IBD and specific associations of cancers such as lymphoma, colorectal cancer, skin cancer and cervical cancer. Thiopurines are associated with specific

additional risks. In IBD cohorts very few thiopurine-related malignancies have been reported. However, studies suggest a relative risk of 4–5 for lymphoma. This still translates to a low actual risk (one extra lymphoma in every 300–1400 years of thiopurine treatment).

Jharap *et al.*[12] published results of an 8-year cohort study to link discontinuation of thiopurines with adverse effects. After five years, only 40% of patients remained on a thiopurine administration, primarily related to the high incidence of adverse effects, with the highest incidence of adverse effects during the first three months of therapy.

Mouse models have been studied to investigate the causative factors relating chronic inflammatory bowel disease to oncologic occurrences. The study suggests the intestinal epithelial cells are susceptible to damage due to prolonged antigen exposure and undergo transcriptional changes that may lead to malignancy.

Multiple studies, including Lewis *et al.*[13] and Askling *et al.*,[14] have proven no inherent increased risk of malignancy or lymphoma with the diagnosis of IBD alone.

Lymphoma and sarcoidosis

Following Brincker and Wilbek's data,[15] epidemiology has established an increased risk of developing various lymphomas in patients with a history of sarcoidosis, with the increased risk quantified broadly, from 5.5 to 11.5 times the average patient risk. The highest risk was established within the Danish population, inclusive of more than 2500 patients, with less than 2% of the case reports later challenged by Brincker himself in literature.[16] Current literature identifies the 'sarcoidosis lymphoma syndrome' to include three key manifestations: sarcoidosis onset 10 years above average median onset age; a sarcoid history followed by lymphoid malignancy; and higher incidence of Hodgkin's. Further, this variation in risk allows for a higher risk in patients with chronic sarcoidosis and those receiving steroid treatment. Presentation varies and may complicate diagnosis and delay appropriate treatment. Patients may present with sarcoid or lymphoma first, and vice versa, or may rarely demonstrate co-existing disease simultaneously. Chemotherapy, such as steroids, has been suggested to exacerbate lymphoma development, which may include non-Hodgkin's. Further, malignancy may develop quickly or over many years. Sites of malignancy may include lungs, liver, skin and reproductive organs of both male and female patients.

Conclusion

Extensive literature review failed to demonstrate linking the co-existence of Crohn's disease and sarcoidosis with malignant lymphomas, as we report in this patient, although theoretically, these three pathologies are interrelated through altered immune responses complicated by current drug therapy. Many clinicians continue to describe either sarcoid or IBD as 'mimicking' the other, so the co-existence may be relatively under-reported. Additionally, the incidence of lymphomas in these patients may pre-exist any treatment, as demonstrated in numerous reports of the sarcoidosis-lymphoma syndrome. We anticipate future studies to evaluate LPD in sarcoid patients not receiving thiopurines and more genetic research to evaluate linkage of the disorders on a histopathological and familial basis. We caution all practitioners in the prescription of thiopurines for the treatment of chronic sarcoidosis and Crohn's and draw attention to the August 2009 FDA black box warning.

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