Case 2. A 50 Year-Old Woman Presenting with Fatigue and Weight Loss

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A 50-year-old female, Ms M, presented to the emergency department and was later admitted to the Medical Teaching unit for investigation of weakness, fatigue and weight loss.

Ms M reported the onset of symptoms over 4-5 weeks. During that time, she had extreme weakness, fatigue and weight loss (accounting for more than 10 percent of her baseline weight) and has had to change her sheets at night secondary to night sweats.

Ms M's past medical history includes common variable immune deficiency (CVID), a type of hypogammaglobulinemia, for which she is followed by an Immunologist. She had a stroke at the age of 33 with no known etiology. This stroke left her with right-sided hemiparesis. Depression. In 2009 she was investigated for iron deficiency anemia with a colonoscopy demonstrating nodular lymphoid hyperplasia. Her medications on admission were lamotrigine, clonazepam, and citalopram. She had no known allergies. She dids not smoke nor drink alcohol.

On examination in the emergency department, her blood pressure was 120/70, heart rate was 96/min, respiratory rate was 12/min and temperature was 37.3. She appeared unwell yet was in no acute distress. She had bilateral palpable, mobile, small, non-tender cervical, right supraclavicular and left axillary lymphadenopathy. Her liver was palpable 5 centimeters below the costal margin. She had a positive Castell's sign. Cardiac and respiratory exams were normal. Neurological exam revealed right-sided weakness that was unchanged from her baseline. Remainder of physical exam was unremarkable.

On admission her white count was 2.2 x 109/L with absolute neutrophil count of 2.0. Her hemoglobin was 98 g/L with MCV of 74.6 fl and platelets were 111 x 109/L. Lactate dehydrogenase was elevated at 398 U/L. Alkaline phosphatase was elevated at 532. The remainder of her admission blood work can be found in Table 1, with note of her quantitative immunoglobulin levels. She had decreased levels of IgG, IgA and IgM.

She was admitted to the Medical Teaching Unit for further work up of her symptoms, pancytopenia and elevated liver enzymes. CT scan of her chest, abdomen and pelvis demonstrated multiple heterogeneous nodal masses within the mesentery and retroperitoneum as well as hypodense lesions in the liver and spleen as well as splenomegaly (Figure 1). A CT guided biopsy of an intra-abdominal mass was preformed which was non-diagnostic. Her serum immunoglobulin levels were measured due to her history of hypogammaglobulinemia and were found to be severely decreased. Treatment with IVIG was initiated. A bone marrow biopsy was performed while in hospital, and was non-diagnostic. Ms. M was discharged from MTU in stable condition with hematology follow up. A subsequent needle biopsy of the liver was positive for diffuse large B cell lymphoma.

She was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) once every 3 weeks for 6-8 cycles. She has now completed 6 cycles of R-CHOP, which was complicated by febrile neutropenia, peripheral neuropathy, and thrombocytopenia, resulting in treatment with Neulasta (to boost white blood cell counts) and a decreased dose of vincristine (to minimize peripheral neuropathy). A PET scan is pending to evaluate response to treatment and help guide further treatment. Ms M has noticed an improvement in her symptoms, although still suffers from fatigue and decreased appetite.

Discussion

This case is a fairly classic presentation of lymphoma. The patients' presentation of fatigue, night sweats, weight loss, and evidence of lymphadenopathy on physical exam were all pointing to this diagnosis. Interestingly she has a history of CVID. This condition is the most common primary immunodeficiency in adults and carries with it a 12-fold increase in risk for the development of lymphoma.[1]

Hypogammaglobulinemia is a term used to denote low serum immunoglobulin (Ig) levels. There are many causes of low Ig in the serum, of which, common variable immune deficiency is the most common form in both adults and children. It is a primary immune deficiency characterized by impaired B cell differentiation/activity leading to diminished antibody production and is found in about 1 in 25000 individuals.[2] It is diagnosed on the basis of:

1) low IgG and low IgA, and/or IgM;
2) poor or absent response to immunizations; and,
3) the absence of another cause for the deficiency.

These broad criteria have led to patients receiving the diagnosis of CVID with dramatically different clinical presentations, hence the term variable.

The most common clinical presentation of CVID is recurrent infections, usually involving the respiratory tract, such as pneumonia and sinusitis. However, given the rise of immunoglobulin measurement for celiac disease, more patients are being diagnosed with no symptoms at all. In symptomatic patients, the severity of disease is quite variable. Some individuals may require intermittent antibiotics while others may present with lung disease (obstructive, interstitial, bronchiectasis, granulomatous), lymphoproliferative disease (splenomegaly, lymphadenopathy), autoimmune disease (autoimmune haemolytic anemia and/or thrompocytopenia, Rheumatoid arthritis), granulomatous disease (can affect any organ system particularly GI, Skin, Respiratory) or even malignancy (most commonly mucosal associated lymphoid tumours and Non-Hodgkin lymphoma) with or without significant history of infection.[2] Thus patients can present with a wide range of symptoms or none at all. Once diagnosed patients should be screened and treated for symptoms (i.e. intravenous immunoglobulin for recurrent infections, or immune modulators for autoimmune disease, understanding there may be an increased risk for severe infection).

Granulomatous disease, splenomegaly, and lymphadenopathy are common to CVID and do not necessarily indicate lymphoma. However, patients with these findings need to be followed closely for possible transformation into lymphoma. CVID increases the risk of developing lymphoma 12 fold with the majority being B-cell non-Hodgkin lymphoma.[1] Biopsies should be obtained to assess for clonal expansion of lymphocytes if there is development of constitutional symptoms (fevers, night sweats, weight loss, or fatigue) or rapid progression of lymphadenopathy. Biopsy is required to distinguish granulomas from lymphoma. Lymphoma will show that the increased cellularity is due to expansion of a single cell clone whereas

Table 1. Blood work on presentation to the emergency department.

Variable	Reference Range	Result
Hemoglobin x 10^9/L	120-160	98
White cell count x 10^9/L	4.5-11.0	2.3
Platelet count x 10^9/L	150-350	111
LDH (U/L)	98-193	398
Creatinine (mcmol/L)	37-96	62
Calcium (mmol/L)	2.23-2.58	2.15
Urea (mmol/L)	2.9-9.3	3.3
Sodium (mmol/L)	136-144	134
Potassium (mmol/L)	3.6-5.1	4.2
Chloride (mmol/L)	101-111	101
Total CO_2 (mmol/L)	22-32	24
Anion Gap	4-16	9
Magnesium (mmol/L)	0.74-1.03	0.77
Phosphorus (mmol/L)	0.76-1.53	1.03
Total protein (g/L)	61-81	45
ALT (U/L)	14-54	34
AST (U/L)	15-41	87
Alk Phos (U/L)	32-92	532
Direct Bilirubin (mcmol/L)	2-9	7
Total Bilirubin (mcmo/L)	0-16	15
Albumin (g/L)	35-50	29
GGT (U/L)	7-50	185
Hepatitis B	Neg	Neg
Hepatitis C	Neg	Neg
HIV	Neg	Neg
IgG	6.50-15.20	2.03
IgA	0.95-3.59	0.36
IgM	0.46-3.04	10.07
C3 (g/L)	0.80-1.64	1.19
C4 (g/L)	0.14-0.35	0.42

`CO_2: carbon dioxide, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transpeptidase.

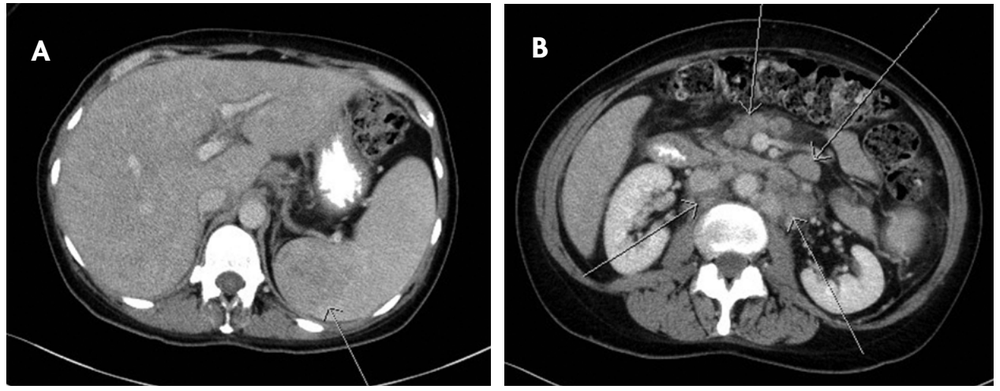

Figure 1. Computed Tomography of patient's abdomen. A. There are diffuse hepatic lesions, a large posterior splenic lesion (arrow), and splenomegaly. B. Diffuse adenopathy can be seen (arrows).

granulomatous tissue will usually show heterogeneous cellular proliferation, which may be driven by chronic infectious stimuli.[2] The presence of both lymphoma and granulomas can sometimes lead to inconclusive biopsy results depending on the tissue sampled. Therefore, if there is a high degree of suspicion multiple biopsies may be required.

There has been much research in the last 10-15 years documenting many different protein mutations important for B maturation/activation that can lead to CVID. It is predominantly thought to be a B cell problem but recent research into CD4+ T cells has demonstrated a subset of CVID patients with a T cell mutation that affects B cell activation. Disease severity depends at least in part on which protein and at what point in B cell maturation it is involved. A consensus study released in 2007 tried to further classify CVID to help predict which patients will likely have a more severe course of disease.[3] They identified a number of specific B cell subpopulations that can be useful in identifying disease severity. Specifically, they found that patients with more severe disease (particularly granulomatous, autoimmune, and lung disease) had a low number (<2% of lymphocytes) of switched memory B cells, meaning they are surface IgM and IgD negative and CD27 positive. This research may help identify patients at risk for granulomatous or autoimmune complications but to date have not revealed therapeutic targets.

Patients diagnosed with CVID should be treated to try to decrease the risk of infection and some of the other complications when signs/symptoms are present. The mainstay of treatment is the use of intravenous immune globulin (IVIG). Since its introduction for the treatment of CVID, the number and severity of infections that patients suffer has been dramatically reduced.[4] However, some patients still suffer more infections than the general population and, although their disease burden is improved, they may require treatment with prophylactic antibiotics. IVIG may also slow the progression of lung functional decline in so affected patients as well as improve autoimmune disease. Unfortunately there has been little benefit demonstrated on other complications related to CVID. IVIG does not seem to help with gastrointestinal complications, granulomas or the risk of progression to lymphoma.

In this case, our patient was known to have CVID and was being followed by an immunologist with routine screening for recurrent infections, autoimmune disease or lung disease. It is likely that the nodular lymphoid hyperplasia that was found on colonoscopy was a gastrointestinal manifestation of her CVID. This finding prompted her referral to immunology and led to the diagnosis of CVID when her Ig levels were low. She was followed yearly and, because she remained otherwise asymptomatic (GI manifestations do not respond well to IVIG) and her Ig levels were only mildly below the 2 standard deviations of the normal mean (normal range), she was not treated with IVIG until her presentation to the MTU. When she presented with the lymphoma her Ig levels were significantly decreased (although she was still not having infectious symptoms), so she was started on IVIG to decrease her risk of developing future infections and complications.

Hypogammaglobulinemia is a relatively common finding in lymphoma and likely results from overgrowth of dysfunctional B cell clones. As CVID may be asymptomatic and therefore go undiagnosed for years, it is difficult to know how many B cell lymphoma patients have premorbid hypogammaglobulinemia. CVID is not uncommon and with increased immunoglobulin testing for diseases like celiac disease the incidence will likely increase in the years to come. It may be asymptomatic, but may also cause morbidity, and patients should be followed and treated if symptoms develop. The development of lymphoma is uncommon but, in patients with a history of CVID and new constitutional symptoms or rapid increase in lymphadenopathy, thorough investigation for malignancy should be undertaken.

Acknowledgement

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