**Case Report**

**Covid-19 Vaccination Immune Response: Bone Marrow Biopsy with Polyclonal Reactive B cell Lymphocytosis: A Case Report**

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**Abstract**

A patient with a recent diagnosis of diffuse large B-cell lymphoma, NOS (not otherwise specified) underwent a staging bone marrow biopsy. The bone marrow biopsy showed a striking reactive polyclonal B cell lymphocytosis without evidence of bone marrow involvement by lymphoma. The etiology for the polyclonal B cell lymphocytosis was unclear until the history of a prior Covid-19 vaccination 49 days prior to the bone marrow biopsy was elicited. The differential diagnosis of reactive polyclonal B cell lymphocytosis is discussed. The importance of including Covid-19 virus vaccination in the differential diagnosis of polyclonal B cell lymphocytosis in the marrow is emphasized, particularly in view of the widespread public health campaign for universal vaccination.

**Keywords:** Bone marrow biopsy;Covid-19; Immune response; Polyclonal B cell lymphocytosis; Vaccination

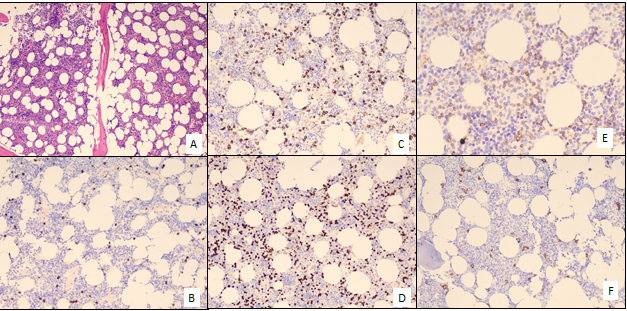
**Introduction**

Polyclonal B cell lymphocytosis, when identified in bone marrow biopsies raises a broad differential diagnoses. The differential diagnosis includes reactions to viral infections, particularly infectious mononucleosis and other chronic infections including mycobacterial infection, cat scratch disease, pertussis, brucellosis, as well as a variety of parasitic infestations. Collagen vascular disease, chronic hypersensitivity and allergic reactions, including drug reactions, and other chronic inflammatory diseases may also result in a polyclonal lymphocytosis. There is also a condition of persistent polyclonal B cell lymphocytosis that has been described. We reported a case of a patient with a diagnosis of diffuse large B-cell lymphoma, NOS who underwent a staging bone marrow biopsy. Although the patient had no evidence for marrow involvement by lymphoma, a striking polyclonal reactive B cell lymphocytosis was identified. There appeared to be no distinct identifiable etiology for this reactive B cell lymphocytosis until it was discovered that the patient had a Covid-19 vaccination 49 days prior to the staging bone marrow biopsy.

**Case Report**

A 40-year-old woman presented with pelvic pain. A pelvic ultrasound examination demonstrated multiple smooth muscle tumors measuring up to 7 cm in size. The patient underwent a hysterectomy with bilateral salpingectomy. On pathologic examination, the smooth muscle tumors were involves by a diffuse large B-cell lymphoma, NOS. An *in situ* hybridization study for EBV (Epstein - Barr Virus) performed on the lymphoma was negative. The lymphoma was found to be of the germinal center type and a double expressor by immunohistochemical stains with overexpression of BCL2 and MYC. However, high-grade B cell lymphoma FISH (fluorescence *in-situ* hybridization) studies showed no rearrangement of BCL2, BCL6, or MYC. In addition, there was no amplification of MYC detected. Therefore, there was no evidence for a double or triple hit lymphoma. Translocation 8; 14 was not detected. A PET CT (positron emission tomography-computed tomography) scan performed following the hysterectomy demonstrated right and left paratracheal lymphadenopathy with increased FDG (F-18 fluorodeoxyglucose) uptake. An 8 cm splenic mass was identified, also with increased FDG uptake.

22 days following a hysterectomy specimen, the patient underwent a staging bone marrow biopsy. In this interval, the patient felt well with minimal pain and had no fevers, night sweats, or weight loss. The bone marrow biopsy showed no evidence of marrow involvement by lymphoma. However, a marked lymphocytosis was identified. Lymphocytes accounted for 31% of the nucleated cells on a 500 cell count bone marrow differential cell count. Immunohistochemical stains on the bone marrow also documented the lymphocytosis. Lymphocytes account for an estimated 20% of the nucleated cells in the marrow. The ratio of T:B cells was 1:3. Plasma cells were estimated at 5%. The lymphocytes had a diffuse interstitial pattern without the formation of lymphocyte aggregates or germinal centers. An EBV *in-situ* hybridization study performed on the bone marrow biopsy was negative. Flow cytometry studies were performed and showed the B cells to be polyclonal with a kappa: lambda ratio of 1.8. The complete blood count at the time of the bone marrow biopsy was unremarkable. There was no evidence for a circulating lymphocytosis. Bone marrow biopsy findings are illustrated in (Figure 1).



**Figure 1:** Photomicrographs of bone marrow biopsy. A) Bone marrow with active hematopoiesis and without overt evidence of lymphoid infiltrate. (Hematoxylin and Eosin; 100 x). B) CD3 immunohistochemistry stain with a normal number of interstitial T cells. (CD3 immunohistochemical stain, 200 x). C) CD20 immunohistochemistry stain with an abnormal increase in interstitial B cells. (CD20 immunohistochemical stain, 200 x). D) PAX5 immunohistochemistry stain confirming an abnormal increase in interstitial B cells. (CD20 immunohistochemical stain, 200 x). E) IgM immunohistochemistry stain showing positive staining of interstitial B cells. (IgM immunohistochemical stain, 400 x). F) CD138 immunohistochemistry stain with normal numbers of interstitial plasma cells. (CD138 immunohistochemical stain, 200 x).

3 days following the bone marrow biopsy the patient developed transient fever and was admitted to the hospital. The complete blood count was unremarkable without lymphocytosis, neutrophilic leukocytosis or left shift. A procalcitonin level was undetectable. A respiratory panel PCR (polymerase chain reaction) study including studies for adenovirus, corona viruses (229 HE, HKU1, NL63, OC43, and SARS Co-2), human *metapneumovirus*, human *rhinovirus*/enterovirus, influenza A and B, parainfluenza viruses [1-4], respiratory syncytial virus, *Bordetella pertussis*, *Bordetella parapertussis*, *chlamydophila pneumonia*, and *mycoplasma pneumonia* was negative. Blood cultures were negative and the patient defervesced on admission and was discharged on hospital day 2 feeling well. The patient was taking no medications other than an occasional acetaminophen or ibuprofen for pain. The etiology for the reactive polyclonal B cell lymphocytosis remained a mystery until it was recognized that the patient was an Ad26.COV2.S Johnson and Johnson Covid-19 vaccine recipient 49 days prior to the bone marrow biopsy. She had no untoward reaction to the vaccination.

**Discussion**

Reactive lymphocytosis has a broad differential diagnosis. Persistent polyclonal B-cell lymphocytosis [1] is a benign, generally indolent disease, which is reported to occur most often in middle-aged women who are cigarette smokers. Although some cases have had an association with Epstein-Barr virus infection, in most cases there is no clear-cut etiologic factor. A characteristic finding in this disease is the presence of circulating binucleate lymphocytes. Unlike patients with persistent polyclonal B-cell lymphocytosis, our patient did not have a circulating lymphocytosis, and was not a smoker. Infectious etiologies may also result in a polyclonal reactive lymphocytosis. Viral infections include Epstein-Barr virus infection, particularly infectious mononucleosis. However, other viral infections including cytomegalovirus, hepatitis viruses, measles, mumps, and rubella for example may also result in a reactive lymphocytosis. *Mycobacterium tuberculosis* infection also may result in a chronic lymphocytosis. Acute bacterial infections result, most often, in an acute neutrophilic leukocytosis, however, there are bacterial infections which can incite a lymphocytosis. Some of these include brucellosis, *Bordetella pertussis*, and *Bartonella henselae*. Finally, lymphocytosis may be associated with a variety of parasitic infestations. Collagen vascular diseases may result in a reactive lymphocytosis. Allergic and hypersensitivity reactions may also result in a lymphocytosis, particularly hypersensitivity reactions to a variety of medications. [2,3] Although this wide spectrum of conditions may result in a reactive lymphocytosis, it is important to recognize that it is typically a reactive T cell predominant lymphocytosis, and not a polyclonal B cell lymphocytosis.

In the patient reported herein, an extensive clinical evaluation for causes of a polyclonal B-cell lymphocytosis was pursued and no apparent etiology for this reaction was identified. However, once it was recognized that the patient had had a Covid-19 vaccination 49 days prior to the bone marrow biopsy, it became apparent that this polyclonal B-cell lymphocytosis was best explained by an immune response to this vaccination. In a study evaluating the immunogenicity of the Johnson and Johnson Ad26.COV2.S vaccine, that this patient received it was found that by day 8 after immunization binding antibodies were detected in 90% of vaccine recipients and neutralizing antibodies were found in 25%. By day, 71 binding and neutralizing antibodies were detected in 100% of vaccine recipients. [4] In a separate study, albeit with a different (Pfizer) Covid-19 vaccine, vaccination resulted in vaccine-induced germinal center B cells, which were maintained at peak frequency in draining lymph nodes for at least 12 weeks duration. [4] It is a reasonable conclusion that the polyclonal B cell lymphocytosis detected in this patient’s bone marrow biopsy on day 49 following vaccination is consistent with an active B cell immunologic response and fits well with the time scale for the evolving immunogenicity of the vaccine.

**Conclusion**

A case of a patient with diffuse large B cell lymphoma, NOS who received the Ad26.COV2.S Johnson and Johnson single Covid-19 vaccine 27 days prior to the diagnosis of lymphoma is reported. 49 days after the vaccination, a staging bone marrow biopsy was performed and it showed no evidence of lymphoma. It did show a polyclonal reactive B cell lymphocytosis which was ascribed to the prior vaccination. Given the public health campaign for universal vaccination, it will be important to recognize this as a cause of a reactive polyclonal B cell lymphocytosis in the bone marrow and include it the differential diagnosis of this condition.

**Patient Consent Information**

The patient in this case report has been completely and entirely de-identified. The author confirms that the absence of this does not in any way detract from the accuracy and value of this case report.

**Declaration of Interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

**Declaration of Interest Statement**

I, Charles M. Lombard, M.D. am entirely self funded and have no financial or personal ties/relationships with any people or organizations that could inappropriately influence this work. I have no competing interests that might influence this work in any way.

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