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CLINICAL VIGNETTE

In Situ Lymphomas

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A 71-year-old female presented with a new left neck mass. The mass had been growing slowly over the last year. Computed Tomography of the neck showed a slight asymmetry in the submandibular glands with left-sided findings being more dramatic than on the right, without discrete mass. Excisional biopsy on the left submandibular gland showed atypical lymphoid proliferation. The atypical cells formed many follicles throughout the gland forming an approximately 2-centimeter mass with focally distorted architecture. The other follicles showed a preserved architecture and reactive germinal centers. The atypical lymphoid infiltrate was cyclin D1-positive, CD5 negative, and, CD10 positive. There was no evidence of lymphoma within the specimen. The cells were negative for t(11;14) rearrangement although a few signals were seen but below threshold for the test. Ig heavy chain testing was negative supporting lack of a malignant clone. These findings were all suggestive of in situ mantle cell lymphoma (MCL).

The patient felt well with no fevers, chills, weight loss, or night sweats. She had a history of hot flashes and chronic arthralgias related to her rheumatoid arthritis. She also had a history of hypertension that was well-controlled with medications, sleep apnea, and pre-diabetes. Her medications included methotrexate, losartan, omeprazole, simvastatin, folic acid, vitamin D, melatonin, and monthly rituximab for her rheumatoid arthritis that was started coincidentally after the lymphadenopathy was noted. Her vital signs and exam were unremarkable.

Mantle cell lymphoma (MCL) is a well-characterized Bcell cancer. It has usually been associated with aggressive clinical disease, poor response to treatment, and pathologic findings including a translocation (11;14) and cyclin D1 overexpression.^{1,2} Over time, it has been determined that there are more indolent forms of the disease that may not require aggressive initial management.¹ Similarly, there have been reports of cells that are positive for cyclin D1 within the mantle zone but otherwise no evidence of overt malignancy.¹ They have been referred to as in situ lymphomas.¹ Specifically, in situ lymphomas have been noted for follicular lymphoma (FL) and MCL.^{1,2} As the name implies, a discrete tumor is not generally noted since the cells do not alter the basic tissue architecture.² Pathologically the mantle zone is thin with no invasion of cells into interfollicular areas.^{2,3} The germinal centers demonstrate hyperplasia with foci of cells staining positive for cyclin D1, CD5, and CD20 in the otherwise normal-appearing mantle zone. CD5-negative cells have also been

described as it may be a later alteration in the disease process.^{2,3} Cyclin D1 overexpression may be an early step in MCL carcinogenesis, and the ultimate lymphoma may require additional mutational events.³ Thus, it has been hypothesized that in situ MCL may be an early event in pathogenesis to MCL.^{1,2}

In situ lymphomas are generally incidental findings in reactive lymph nodes.^{1,2} Commonly the pathology is found in nodes but reports have noted disease in other areas with lymphoid tissue such as the oro- or nasopharynx, intestines, and spleen.^{1,3} The exact incidence of in situ MCL is not known.¹ One group stained for cyclin D1 in one hundred specimens with reactive follicular hyperplasia with none testing positive.¹ Conversely, another study testing for in situ FL during evaluation for follicular hyperplasia found 2.5% of samples with in situ FL.² These reports support the relative rarity of in situ lymphoma.

While some presume in situ MCL may precede MCL, most accounts actually suggest in situ lymphoma has an indolent nature with rare evolution into lymphoma.³ However, data have been limited, and the risk of progression to overt lymphoma is not clear.¹⁻³ There are no recommendations for treatment of in situ disease.^{2,3} Given the rarity, there are no guidelines for follow up.² It can also be difficult even with tissue review to discriminate in situ lymphoma from early lymphoma.² It is imperative that all cases of in situ lymphoma be evaluated with imaging, labs and bone marrow biopsies to rule out the possibility of lymphoma.^{2,3} The consensus of previous reports suggests close follow up and work up of any new lymphadenopathy for the possibility of subsequent lymphoma.²

The literature for in situ mantle cell lymphoma did not mention testing for t(11;14). One report did note that all eight cases did manifest the translocation and were cyclin D1 positive.³ This was unusual in that a distinct mass was noted on pathology albeit not imaging, unlike most cases of in situ lymphoma. However, architecture was otherwise preserved with no cell invasion, important hallmarks for in situ MCL. While the cells were cyclin D1 positive, there was no definitive presence of t(11;14). Whether the lack of this translocation indicates earlier presentation of biologic disease is not known. As recommended by all guidelines, a Positron Emission Topography was done to rule out the possibility of occult lymphadenopathy and showed no evidence of lymphoma. Her complete blood count was normal as were other basic laboratories. A bone marrow biopsy was deferred given the normal imaging and labs and low suspicion for marrow disease.

It was recommended that she continue close follow up for exams and labs with no new abnormalities noted during the subsequent year. Interestingly, she did have a concomitant rheumatologic illness for which she had recently started monthly rituximab, a drug commonly used for MCL as well. Whether this would affect long-term prognosis is impossible to know.

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