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CORR Insights®: Pathologically Benign Lymph Nodes Can Mimic Malignancy on Imaging in Patients With Angiomatoid Fibrous Histiocytoma

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Where Are We Now?

Some soft-tissue tumors are associated with a low potential for lymphonodular metastasis. Myxoinflammatory fibroblastic sarcomas and plexiform fibrohistiocytic tumors [4, 9] are two such diseases;

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angiomatoid fibrous histiocytoma (AFH) is another. It is important to recognize that although nodal metastases are rare, they do occur, and it is this potential that makes diagnosis and treatment of patients with AFH so challenging.

For patients with enlarged lymph nodes, surgeons, oncologists, radiologists, and pathologists considering resection must weigh the risk of overtreatment (since most of these patients will not have nodal metastases) against the risk of undertreatment (as a few patients will develop such metastases and become incurable [12]). By contrast, although lymph node dissection is a rather straightforward procedure, it still can cause perioperative morbidity,

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and axillary and inguinal lymph node dissection may lead to chronic lymphedema, recurrent erysipelas, and poor quality of life [10]. Therefore, unnecessary lymph node dissection should be avoided.

The challenge for clinicians treating malignancies is finding the right balance of therapy. Common tumors such as breast or colonic cancers often accumulate large patient numbers for potential studies, making it easier to establish guidelines for the statistically best therapy. But because AFH is a rare disease, clinicians must make a decision on an individual basis, with little evidence to help guide them. The current study by Ulaner and colleagues is important because it gives a rough estimation of how often lymph node metastases occur and how they might be detected.

How to properly detect nodal metastases has long been under investigation [3, 13], leading to a sensitivity and specificity around 75% for both CT and MRI. The main criterion of malignancy in CT and MRI is the size of the

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lymph node; if the diameter in the short axis exceeds a certain cut-off, the lymph node will likely be suspected of malignancy. In fludeoxyglucose-positron emission tomography (FDG-PET) scans, elevated uptake values are a sign of malignancy [6]. FDG-PET scans are also useful for staging other sarcomas [11]. However, AFH has the peculiar property of causing lymphadenopathy and systemic symptoms likely due to the production of cytokines by neoplastic cells [5]. This reactive lymph node activation may cause an elevated FDG uptake, potentially leading to the discovery of suspicious, but benign, lymph nodes on both MRI and FDG-PET/CT imaging.

Where Do We Need To Go?

A standardized diagnostic algorithm for AFH and similarly rare low-grade sarcomas has not yet been established. It is widely agreed that complete surgical resection of the primary tumor should be performed, and it seems sensible to resect single metastases, if possible. However, case numbers have been too small to perform prospective trials. We do have retrospective analyses and case reports, which review how AFH might be staged and treated [2, 8]. But is MRI, FDG PET/CT, or a combination of both, the best method to detect metastatic disease? When considering costs of

extensive diagnostic procedures, aggressive surgical treatment of lymphadenopathy, and possible side effects on one side, and the severe consequences of undertreatment on the other, this question is key.

In the current study, Ulaner and colleagues suggest performing image-guided biopsies of suspicious lymph nodes to avoid overtherapy. But can AFH metastases be reliably detected in needle biopsy specimens? Would smaller metastases be missed? This will likely depend on the size of the biopsy and on the location of the suspicious lymph nodes. For example, retroperitoneal nodes might be more difficult to reach than inguinal or cubital nodes. Lymph node biopsy is a less invasive and more cost-effective method than lymph node excision, but it might be less sensitive.

How Do We Get There?

Ideally, multicenter (or even multinational) studies would offer the sufficient number of patients necessary to obtain valid data for rare tumors like AFH. In order to increase effectiveness and efficacy of such a collaboration, other rare sarcomas should be included in the study as well.

If multicenter studies are not feasible, a prospective study design with standardized diagnostic and therapeutic

pathways would be a solid alternative. The advantages of being examined and treated within the framework of a study should be pointed out to the patients in order to prevent them from dropping out and to achieve sufficiently high case numbers.

Rare diseases, particularly sarcomas, should be treated by surgeons, radiologists, oncologists, and pathologists at centers with experience in the treatment of those conditions. The histopathological diagnosis of sarcomas like AFH is not easy to make and should not be based on hematoxylin and eosin morphology alone. Since there are no reliable immunohistochemical markers, detection of the established gene rearrangements by fluorescence in-situ hybridization (FISH) should be mandatory [1, 7]. Central pathology review seems sensible, but not indispensable if all participating centers agree upon a standardized histopathological workup and all centers provide FISH testing. The correct histopathological diagnosis (and potentially genetic subclassification) is crucial for the validity of rare tumor studies because a single misclassified patient (such as a high-grade sarcoma mistakenly included in a low-grade sarcoma study), may completely distort the results.

Likewise, imaging procedures should be standardized. If our study is comparing MRI, PET/CT, and potentially ultrasound, these imaging techniques should be performed in

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each patient to facilitate a full evaluation. The diameters of all detectable lymph nodes and the degree of radionuclide uptake should be collected, and these data points should be correlated to histopathologic results by receiver operating characteristic (ROC) curve analysis in order to find an ideal threshold value for the distinction between benign and malignant lymph nodes—as opposed to setting arbitrary threshold values in advance. The timing of the imaging procedures may be crucial since there is evidence that lymph node activation can lead to false-positive interpretation of metastatic disease due to cytokine production by the primary AFH. If this occurs, researchers should investigate whether nonmetastatic lymph nodes regress after resection of the primary tumor. Imaging should be performed sometime after tumor removal, when unspecific inflammatory effects accompanying surgery have faded. Additionally, because AFH is a slowly growing tumor, it is unlikely to become incurable in the latency between primary surgery and imaging.

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