Benign lymph node inclusions mimicking metastatic carcinoma

Although previously well recognised, Fisher et al have highlighted the importance of differentiating between metastatic carcinoma and benign intranodal epithelial invasion. I describe three further cases encountered recently in which immunocytochemical analysis provided valuable evidence to help clarify the nature of intranodal inclusions. In each case the differentiation was clinically critical in that no other nodes were involved.

Case 1
A 66 year old woman had a mass in the left breast detected by screening. A localisation biopsy specimen showed a grade 1 ductal carcinoma and a diffusely infiltrating lobular carcinoma. She underwent mastectomy: there was residual invasive lobular carcinoma and multiquadrant foci of invasive lobular carcinoma up to 7 mm diameter. The original tumour was estimated at 200 mm diameter and there was pagetoid spread of lobular carcinoma in ducts and extensive vascular invasion. Three of 12 axillary lymph nodes contained groups of small cells in the capsule. Initially thought to be metastatic lobular carcinoma, immunocytochemistry was performed to look for lesser degrees of spread to the lymph nodes in the same slide. Immunocytochemistry was performed on the breast tumour and the lymph nodes for HMFG-2 AE1/AE3, CAM 5.2, and S100. The lobular carcinoma stained strongly positively for AE1/AE3, CAM 5.2, and HMFG 2, and weakly for S100. Cells in the lymph node stained strongly for S100 but were otherwise negative, indicating that they were benign nerve cells. Interestingly, there were numerous S100 positive cells scattered through the lymph node parenchyma.

Case 2
A 65 year old woman had a cytologically malignant lump detected by screening in the left breast. She underwent mastectomy and histological examination showed a 14 mm lobular carcinoma. One of 17 axillary lymph nodes contained a suspicious focus of sclerosis and scattered histioctye-like cells with clear cytoplasm. Periodic acid Schiff stain showed intracytoplasmic mucin, and immunocytochemical staining showed positivity for HMFG-2 and CAM 5.2 and was negative for carcinoembryonic antigen (CEA) in both intranodal cells and the original carcinoma, confirming metastatic lobular carcinoma (fig 1).

Case 3
A 26 year old woman had bilateral papillary serous cystadenomas of the ovaries of borderline malignancy. Two unequivocal stromal invasion was seen, but tumour was present on the surface of the left ovary. The right external iliac lymph node was excised. Histological analysis showed a single large lymph node in which there were multiple subcapsular epithelial structures, some of which showed papillary structure with psammoma body formation. These were thought to be benign inclusions of Mullerian type epithelium (fig 2). In an attempt to demonstrate disparity in immunocytochemical profile to support this diagnosis immunocytochemistry was performed on both ovarian tumours and the lymph node for CEA, vimentin, HMFG-2, S100, CAM 5.2 and AE1/AE3. The immunocytochemical markers were similar in the ovarian tumours and inclusions except that CA125 showed delicate membrane staining in both ovarian tumours but the epithelial structures in the lymph nodes did not stain.

In each of the cases described the lymph node diagnosis made the difference between lymph node positive and lymph node negative, with subsequent implications for clinical management. The cases illustrate the use of immunocytochemistry to support or refute a morphologically based opinion. The first case showed that nerve cell inclusions can line up in a pseudo-Indian file looking remarkably like metastatic lobular...
carcinoma, as emphasised by Fisher et al., and that metastasis seemed plausible in this case in view of the extensive primary tumour and lymphatic invasion. In retrospect, the intracapsular location should have led to the exercise of caution. The case also shows the phenomenon of intranodal naevus cells as well as the more commonly recognised intracapsular location.

The second case raises the question of whether lymph nodes in cases of lobular carcinoma of the breast should be screened for metastatic disease using immunocytochemistry. Presence of single cell micrometastases has been shown to have prognostic value. Clearly the routine use of serial sectioning or immunocytochemistry to detect metastatic disease is impracticable in ordinary practice but judicial use in individual cases can be very helpful. It is important to recognise that breast carcinomas may be S100 positive (as in case 1) and a matching of immunocytochemical profile between primary and secondary tumours is essential.

The third case is an example of a long recognised problem beautifully described and illustrated by Ehrmann et al and one which is impossible to resolve on purely morphological grounds. Immunocytochemical profiles of ovarian carcinoma and epithelial inclusions would be expected to be similar but in this instance tumour positivity for CA125 provided some support for the morphological opinion that the lymph node inclusions were benign. CA125 has proved not to be specific for ovarian carcinoma. Mesothelial cells seem to require inflammatory cytokines for CA125 expression and this expression tends to be apical.

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Dr Mills et al comment:
We are pleased that our paper stimulated Douglas-Jones to present three further cases where immunohistochemistry was helpful in resolving the nature of difficult intranodal lesions. It is interesting to note in his first case that numerous S100 positive cells scattered throughout the lymph node parenchyma were considered to be intranodal naevus cells. The possibility that these cells represent dendrocytes, which are known to stain strongly for S100 (and also, sometimes, but less consistently, for CAM 5.2) should also be considered.

In case 2 small deposits of metastatic lobular carcinoma were detected and, as stated, the presence of micrometastases has been shown in a few studies to be of prognostic value. However, there are many conflicting papers. Furthermore, one of the groups with a positive result has subsequently reported that, in the case of lobular carcinoma, immunohistochemically detected micrometastases are of no relevance.

Case 3 is particularly intriguing and it seems that here the diagnosis was based mainly on morphology. Quite rightly, little weight was placed on the discrepant staining between the tumour and supposed nodal inclusion. Staining for CA125 can be very heterogeneous.

As emphasised by Douglas-Jones it is always important to use a panel of antibodies to evaluate an immunocytochemical profile when making a differential diagnosis.


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