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Review

Granulomatous inflammation in lymph nodes draining cancer: A coincidence or a significant association

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Granulomatous inflammation is considered to be an immune mechanism against infections or certain non-neoplastic conditions. Rarely granuloma formation may be noted in neoplastic disorders also. However a granulomatous response in the lymph nodes draining cancers is unusual. Such granulomas may sometimes show tumour cells in their centre. The exact cause of this phenomenon is not known but an immunologic reaction to tumour antigens has been suggested. A close scrutiny of such granuloma is necessary to avoid under diagnosis of a metastatic disease. Subtle morphological features which may be helpful in differentiating a co-existing infection or tumour induced granuloma need to be addressed. Moreover the biologic significance of such a granulomatous response in inducing tumour remission or in shielding tumour cells from host lymphocytes also requires further investigation.

Key words: Granuloma, cancer, metastasis.

INTRODUCTION

Diagnosis of granulomatous inflammation is a common practice in pathology. The common causes of granulomatous reaction are infective agents like mycobacteria, fungi, parasites e.t.c and non-infective aetiologies like sarcoidosis, foreign bodies, wegener's granulomatosis, Crohn's disease e.t.c. In addition, certain neoplasms are also known to be associated with a granulomatous response in the parenchyma e.g. Hodgkin's disease and non-Hodgkin T cell lymphomas, seminoma of the testis, renal cell carcinoma, nasopharyngeal carcinoma and ovarian dysgerminoma (Kumar et al., 2005; Coyne, 2002; Coyne, 2002; Hes et al., 2003; Chen et al., 1991). In some of these malignancies for example, Hodgkin's disease the granuloma may be the dominant presentation of the primary disease (Daly et al., 1998). The presence of granulomas in tumour parenchyma has largely been attributed to the cytokine milieu of either the main tumour or the other cells composing the tumour background (Haralambieva et al., 2004).

In other cases the granulomatous inflammation may be found in the lymph nodes draining the primary tumour either with or without metastatic cancer. This phenomenon has been variously labelled as sarcoid reaction or sarcoid like lymphadenopathy by different authors (Gregori et al., 1962). It has been observed in many malignancies e.g. breast carcinoma, gastric, colonic and laryngeal cancer (Ophir et al., 1985; Bigotti et al., 2002) etc. In Hodgkin's disease the granulomas have been observed in liver and spleen which exhibit no evidence of Hodgkin's disease involvement. In few instances the cause of granulomatous reaction (e.g. a therapeutic agent; that is, BCG, Inter-feron, Methotrexate) can be discerned. Sometimes a coincidental association of a systemic granulomatous disease and a malignant neoplasm may be the cause (Patel et al., 1977). In many other cases the aetiology of granulomas remains obscure. Few questions therefore need to be addressed regarding this interesting observa-tion.

What are the factors governing the granuloma formation at these sites?

The main causes of granulomatous reaction at the drainage sites of malignancies may be:

1) Idiopathic
2) Foreign body reaction to necrotic tumour or a previous procedure.

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3) Therapy related granulomas
4) Metastasis
5) Associated systemic illness like tuberculosis, sarcoidosis etc.

In majority of the cases no definite cause can be found and aetiology remains obscure. Some authors suggest the possibility of T- cell mediated immunological reaction to soluble antigens shed by the tumour which leads to a granulomatous response whereas others attribute it to persistence of a nondegradable product (Kobayashi et al., 2001). The tumour -related sarcoid reactions occur at the characteristic sites of sinus and especially T-zone in lymph nodes and are composed of different inflammatory cells within granulomas. The latter contain mature dendritic cells and T lymphocytes (Kurata et al., 2005). Hojo et al. (2000) in their study observed more number of CD4-positive cells in internal area of granuloma than the surroundings which predominantly showed CD8- positive cells, the same distribution pattern as observed in sarcoidosis. Santini et al. (1992) reported presence of epithelioid granulomatous reaction with amyloid deposition in lymph nodes draining invasive breast (Santini et al., 1992). The immunology can be ex-plained by production of Interferon (IFN-) by local natural killer (NK) and T cells infiltrating the tumour which further activate the den-dritic cells. Antigen-loaded dendritic cells produce inter-leukin 12 (IL-12) and present antigen to naive $CD4^+$ T cells which differentiate into T helper 1 (Th1) cells. Within hours to days after antigen exposure, activated Th1 $CD4^+$ cells interact with activated macrophages leading to production of IFN- and, which results in further maturation of macrophages and granuloma formation. However what precise antigens in the above malignancies play a role in granuloma formation is not clearly known (Sneller, 2002). Some other mechanisms like foreign body reaction to necrotic material in the tumour or secondary to some procedure performed have also been suggested as the probable causes (Coyne, 2002). Some commonly used cancer treatment agents may also evoke a granulomatous response. Intravesical B CG therapy for treatment of bladder cancer may some-times lead to extensive granulomatosis. Exogenously administered interferon- and may activate production of interferon- and the expres-sion of mRNA coding for IL-12, which leads to Th1 differentiation and hence granuloma formation (Kamel et al., 2004).

Should the patient be investigated for causes of granulomatous pathology including tuberculosis?

An infectious aetiology for a granuloma is rarely seen. Kennedy et al. (2008) noted infectious pathology in 1 out of 9 patients of lung cancer with mediastinal lymph nodal granulomas (Kennedy et al., 2008).

In all cases a search for acid fast bacilli is not required. However, if clinical symptomatology suggests a co-existing infection an investigation for tuberculosis should be done. In endemic areas where tuberculosis is rampant a PCR based testing for tuberculosis may be carried out (Khurram et al., 2007). Association of carcinoma with other systemic disease producing granulomas is also rare with only case reports available (Yamasawa et al., 2000).

Do these granulomas at the drainage site signify presence of an occult metastasis or an impending metastasis?

Some of the older reports have shown an association of epithelioid granulomas with tumour metastasis in the lymph nodes (Hes et al., 2003). Coyne et al. (2005) in their study on 4 cases of breast cancer noted the presence of necrotic malignant cells in the granulomas present in draining nodes. A close scrutiny of such granulomas is therefore necessary to avoid under diagnosis of the metastatic disease. Granulomatous inflamation has been described in association with micro- invasive breast carcinomas, for example in carcinoma *in situ* with invasive foci measuring <1 mm and in relation to microscopic foci of colonic carcinoma within perivascular mesenteric fat (Coyne et al., 2005; Coyne and Haboubi, 1992). In Hodgkin's disease the granulomas may sometimes precede the onset of the primary malignancy (Daly et al., 1998). However it may not be easy to identify the tumour cells in the lymph node and immunostaining with cytokeratin may be required for recognizing these (Coyne and Haboubi, 1994).

Is there any prognostic importance attached with the granuloma formation at the drainage site?

The prognostic significance of these granulomas is currently not known. Tomimaru et al. (2007) in their study on lung cancer patients did not find any prognostic difference between the cases with and without sarcoid reaction. Whether these are formed to mechanically shield and protect the cancer cells from host immune cells at the metastatic site or they represent a good host immune response to tumour remains to be investigated. A large series on this phenomenon may perhaps help to identify the true incidence and prognostic importance of granulomas in draining lymph nodes of a carcinoma.

Are there any features which help to differentiate between granulomas associated with metastasis and granulomas without metastasis?

The tumour metastasis to draining lymph node may be seen as extensive deposits (Figure 1), completely replacing the nodal parenchyma or it may just be represented by subtle subcapsular emboli (Figure 2). The granuloma whenever seen may be present with or without tumour deposits within the lymph node. The morpho-

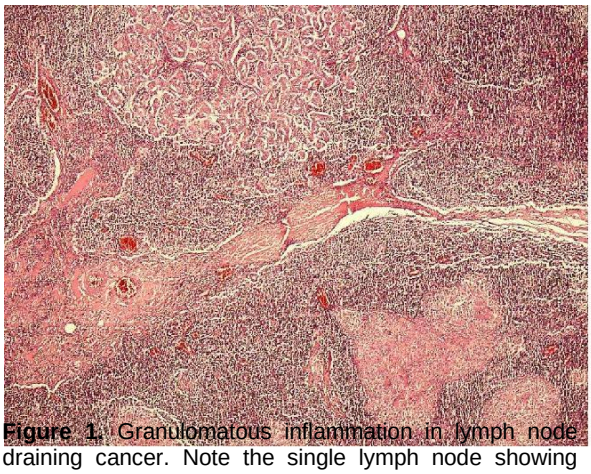

Figure 1. Granulomatous inflammation in lymph node draining cancer. Note the single lymph node showing epithelioid cell granulomas and breast cancer metastasis (H and E staining).

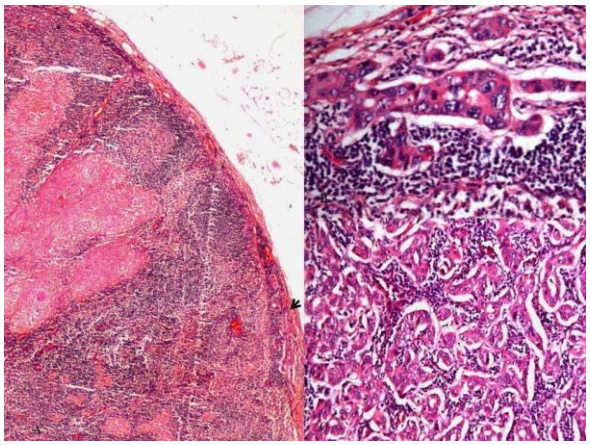

Figure 2. Patterns of cancer metastasis in the lymph node with granulomatous inflammation (H and E staining) A) Cancer emboli in subcapsular sinus (arrow) with underlying granulomas in nodal parenchyma B) High power view to appreciate the malignant cells. There were no other metastatic foci in the lymph node apart from those in sinus C) Florid metastasis of breast cancer in the nodal parenchyma.

logy of such granuloma is no different from benign causes of granulomatous inflammation either on light or electron microscopy. The resemblance to sarcoid granulomas has prompted some authors to label them as sarcoid-like granulomas. They may be small to large and confluent, with many giant cells both of foreign body and Langhan's type. Fibrinoid necrosis may or may not be present however large areas of confluent caseation necrosis generally are not found (Figure 3). Calcification and asteroid bodies may also be seen. A careful search under the microscope may reveal the presence of malignant cells. However, sometimes it may be difficult to identify the tumour cells in these nodes with haematoxylin and

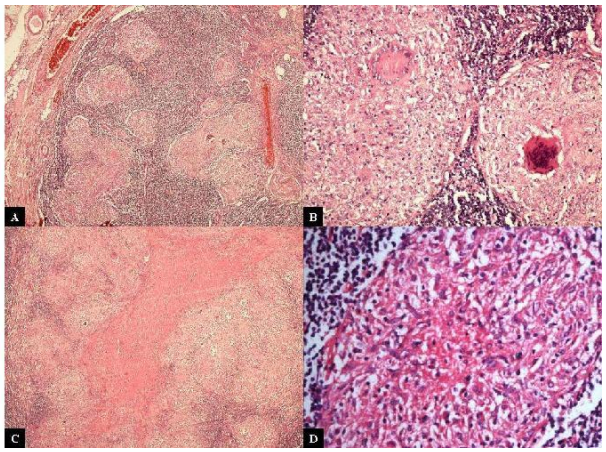

Figure 3. Types of granulomas seen in lymph nodes draining cancer A) varying sized granulomas becoming confluent at places B) granulomas may show both foreign body and Langhan's type giant cells C) large granuloma with central necrosis of fibrinoid type. Note the absence of typical caseation necrosis seen in tuberculosis. D) sarcoid-like granuloma composed of epithelioid cells and lymphocytes. No malignant cells are noted in this granuloma (H and E staining).

eosin stain alone and immunohistochemistry is required (Syrjanen, 1981). Mustafa et al. (2006) in their study on immunohistochemistry of tubercular lymph-adenitis showed increased expression of IL-10 and TGF - with decreased expression of TNF- and IFN- to be responsible for necrosis and tissue damage. The cytokine profile of malignancy associated granuloma however remains to be studied. Future studies may help to high-light the differences, if any, between a benign granuloma and malignancy associated granulomata. Clinical history of stony hard lymph node may give some clue regarding the underlying malignancy.

To conclude, carcinoma specially arising from breast, stomach, colon and larynx can be associated with a granulomatous response in the draining lymph nodes and should be included in the list of differential diagnosis of causes of granulomatous inflammation. Although infection associated granulomatous inflammation may coexist however tumour induced granuloma in the draining lymph node can be easily differentiated from those secondary to infection. Whenever a granuloma is seen in the draining lymph node in a known case of cancer it should be carefully scrutinized for the presence of malignant cells. Whether these granulomas represent an already existing or an impending metastasis in malignancies needs to be investigated. Possible diagnostic, prognostic and therapeutic ramifications of this phenomenon are open for further research.

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