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Review Article

Malignancy and Granulomatosis: Causality or Coincidence? Narrative Systematic Review

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ABSTRACT

In patients with malignancy, the common etiologies of granuloma formation are tumor related sarcoid reaction, sarcoidosis, tuberculosis and other granulomatous diseases. Often, the finding of granulomas in malignant patients may obscure the primary malignancy or may mislead towards treatment of infectious and other etiologies. Hence, their proper recognition and necessary follow up is needed to establish the cause of granulomatous lesions and for proper management of patients.

Keywords: **Granuloma, Cancer, India**

Introduction

Granulomatous inflammation is considered an immunological response against infections or certain non-neoplastic conditions (1). Occasionally, granulomatous reaction may also occur within the primary neoplasm, in regional lymph nodes either involved or uninvolved by tumor, in sites of distant metastasis, or in uninvolved organs (2). Relationship between granulomatosis and malignancy has been suspected for a long time (3-9) but still the cause of this relationship is unknown. It is most likely due to immunological response to soluble tumor related antigens (10). Other etiologies of granuloma formation in patients with malignancy are co-existing systemic granulomatosis pathology, infective etiology, and reaction to therapeutic drug or procedure (1). Here we provide a comprehensive review of association between granulomatosis and malignancy.

Granulomas in Association with Malignancy

Certain neoplasms are known to be associated with granulomatous response in parenchyma like Hodgkin disease, non-Hodgkin lymphoma, seminoma of testis, renal cell carcinoma, nasopharyngeal carcinoma and ovarian dysgerminoma (10-14). More rarely, granulomas may also occur within the stroma of breast, renal, hepatocellular (15-18) and colonic carcinoma (10). Occasionally, granulomatous inflammation may be found in lymph node draining the primary tumor with or without metastatic involvement. This phenomenon has been labeled as "sarcoid reaction" or "sarcoid-like lymphadenopathy" (19-21). Sarcoid reaction occur in 4.4% of carcinomas, 13.8% of patients with Hodgkin disease, 7.3% of cases with non-Hodgkin lymphoma, 50% of seminomas and 0.4% of sarcomas (2,5). It has also been observed in breast, gastric, colonic and laryngeal

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cancer (22, 23) along with head and neck cancer (24). By definition, to label a granuloma as tumor related sarcoid reaction, patient should not have sign and symptoms suggesting other granulomatous pathologies including systemic sarcoidosis (1).

Most probably, sarcoid reactions are caused by immunological hypersensitivity to antigens derived from tumor cell leading to granuloma formation (25). It may be marker of immunological antitumor response of macrophages activated by T- lymphocytes. These tumor related sarcoid reaction occur at T- zones of lymph nodes. It was seen by Kurata *et al.* (26) that solitary granulomas first occur between lymph sinus and T- zone and multiple granulomas mainly occur in T- zone, whereas confluent type occupy the whole node except residual follicles. This pattern suggests a continuous spread and growth of granuloma along T- zone where antigen presentation occurs. Antigen loaded dendritic cells produce IL-12 and present antigen to CD4+ cells which differentiate into T-helper 1(Th1) cells. Activated Th1CD4+ cell interact with activated macrophages causing production of interferon- gamma leading to granuloma formation. However which precise tumor antigen plays a role in granuloma formation is still not clearly known (27). Hojo *et al.* (28) observed more number of CD4+ cells in internal area of granuloma than surroundings which predominantly showed CD8 + cells, same distribution pattern as seen in sarcoidosis. Similar to sarcoidosis, angiotensin 1- converting enzyme was a constant finding in epithelioid and giant cells suggesting a common inflammatory pathway.

Sarcoid like granulomas may be seen in draining nodes with extensive deposits or simply subtle sub-capsular emboli. Sometimes, no evidence of tumor emboli is seen within lymph node and immunohistochemistry is required to demonstrate small tumor deposits (29). In patients with carcinoma, sarcoid reactions occur about four times more often in regional lymph nodes without metastasis than in those containing metastasis (1). In few studies, these granulomas at drainage site were associated with metastasis even in occult primary like micro-invasive breast carcinoma or carcinoma-in-situ of colonic carcinoma (30, 31). Nozoe *et al.* (32) in their study could not find metastatic deposits in lymph node bearing sarcoid reactions in cases of colorectal carcinoma despite large size of primary tumor. So, in absence of known primary malignancy or evidence of metastasis in lymph nodes, presence of these granulomas may be wrongly attributed to being caused by other granulomatous etiologies. Whether these granulomas are formed to mechanically shield and protect cancer cells from host immune cells at metastatic site or they represent a good host response to tumor is still a debatable topic.

The prognostic importance of these granulomas is currently debatable. In Hodgkin disease, these granulomas may be primary presentation at various sites without evidence of malignancy in those sites. Their sole presence does not imply subsequent relapse of disease in a site involved with granulomas in absence of Hodgkin disease in that site. O' Connell *et al.* (33), Sacks *et al.* (34) and Brincker (35) in their respective studies concluded that presence of granulomatous response in patients with Hodgkin disease correlated with improved survival in all stages of disease. Similarly in gastric adenocarcinoma, there is evidence that patients with sarcoid reaction have better prognosis (5, 34, 36). However, Tomimary *et al.* (37) in their study on lung cancer patients did not find any prognostic difference between cases with or without sarcoid reaction. Still in majority of neoplasms, their status as that of occult or impending metastasis is controversial and requires large series to attach prognostic importance to these granulomas.

Co-Existence of Malignancy and Sarcoidosis

Patients may rarely present with typical sarcoidosis occurring before, during or after diagnosis of malignancy. Recent studies have documented such association with various malignancies (6, 24, 38). Some authors propose the term 'cancer-sarcoid syndrome' to appoint association between the two (39). The association between sarcoidosis and malignancies like melanoma (6, 40-42), lung cancer (7, 25, 43, 44), testicular germ cell tumor (45-47), renal cell carcinoma (17, 48, 49), hepatocellular carcinoma (6, 50-52), digestive tract cancer (53, 54) has been investigated and established by various authors in their studies respectively

In 1986, Brincker for the first time described association between systemic sarcoidosis and malignant lymphoma and used the term "Sarcoidosis-lymphoma syndrome" for this association (55). It refers to development of lymphoma at least 1-2 years after diagnosis of sarcoidosis. It also includes patients with sarcoidosis who develop other hematological malignancies (38). In addition, it also includes patients with lymphoma and hematological malignancies subsequently develop sarcoidosis. Sarcoidosis and lymphoma may occur together with sarcoidosis preceeding lymphoma in most cases (56). The increased prevalence of granulomatous disease during the malignant hemopathies is well established especially for Hodgkin disease (14%) but also for NHL (4-7%) (55-58). Other malignant lymphoproliferative diseases including B-cell lymphoma, CML and CLL are also often seen among patients affected by sarcoidosis (55, 59). The organ areas affected by granulomatous reaction can also contain neoplastic infilteration making interpretation quite difficult of two pathologies. Because many features of sarcoidosis and lymphoma are similar, histological confirmation of malignancy is necessary, especially if new nodal disease and splenomegaly are present.

Co-Existence of Malignancy and Infective Granulomatous Etiologies

Common infective agents including mycobacteria, toxoplasmosis, fungi, parasite can also evoke granulomatous response in malignant patients. The granulomas in mycobacterial infections are well demarcated and caseating while those of toxoplasmosis are often poorly defined microgranuloma. Most intriguing association is between tuberculosis and malignancy (60-62). Bayle first described the association of tuberculosis and malignancy in 1810. He describes "cavitation cancereuse" as one of the various types of tuberculosis, which appears to be the first published description of co-existence of the two (63). Although, both entities are well documented and common, the co-existence of two is relatively less documented (64).

The development of mycobacterial infections in patients with immunocompromised condition caused by malignancy is well known. In recent studies, tuberculosis has been postulated as risk factor for development of malignant tumors (65-78); the malignancies include B-cell lymphoma, squamous cell and small cell carcinoma of lung. Chronic inflammation caused by mycobacteria is being speculated to create malignancy by inducing cellular turnover, causing direct DNA damage and also enhancing anti-apoptotic activity. Scar cancer of lung created by tuberculosis is another example of possible association. Tuberculosis and various malignancies mimic each other and can have atypical clinical or radiological expressions like palpable lymph nodes due to lymphadenitis may lead to over-staging of TNM system. Similarly, missing the diagnosis of tuberculsis in patients with malignancy can deteriorate the underlying infection and can cause dissemination of infection particularly with commencement of immunosuppressive therapy. Thus, the diagnosis of tuberculosis infection in setting of malignancy requires high index of suspicion and proper management.

Role of Antineoplastic Therapy in Causation of Granuloma

Immunotherapy such as interferon and IL-2 used in treatment of malignancy has been reported to induce systemic sarcoidosis like pathology, probably by reproducing some physiological mechanisms involved in sarcoidosis (79-82). Although etio-pathogenesis of systemic sarcoidosis is yet unknown, the role of inflammatory mediators such as IL-2 and IFN are probably involved. Hence, IFN given in pharmacological dose could cause macrophage activation leading to granulomatous response. To date, alpha interferon appears to be the most common agent that causes sarcoidosis in patients treated for malignancies, although agents like cisplatin is also known to create sarcoid like granulomatous response.

Diagnostic Dilemmas of Granulomatosis in Malignancy

Both infective and sarcoid-like granulomas can be seen in draining lymph nodes of patients with malignancy. The clinical features of peripheral lymphadenopathy caused by tuberculosis are similar to those caused by malignancy. In both cases, patients may present with a painless swelling. Hence, fine needle aspiration cytology or biopsy examination is required for confirmed diagnosis. Often, the finding of granulomas in malignant patients may obscure the primary malignancy or may mislead towards treatment of infectious etiologies. Hence, their proper recognition is essential for prognostic and management purpose. The differentiating features between granulomas caused by both pathologies are given in Table 1.

Table 1: The differentiating features between sarcoid like granuloma and infective granuloma

Features	Sarcoid like granulomas	Infective granulomas (prototype tuberculosis)
Association with metastasis	May be present with or without metastasis	Can be seen independent of metastatic status of patient
Granulomas	Resembles granulomas in sarcoidosis, small or large, sometimes confluent	Discrete granulomas resembling tuberculosis with or without associated necrosis
Foreign body/langhans giant cells	+/-	+/-
Necrosis	Fibrinoid necrosis +/-	Caseous necrosis +/-
Calcification	May be seen	Generally absent
Asteroid bodies	May be seen	Generally absent
AFB staining	Negative	+/-

As extensively reviewed and recently discussed, malignant disorders are also reported in patients with sarcoidosis and conversely, sarcoidosis also occur in patients after diagnosis of malignancy. To differentiate between granuloma of systemic sarcoidosis and sarcoid like granulomas in patients with malignancy on basis of morphology alone is difficult. Diagnosis of systemic sarcoidosis is most securely established when well recognized clinico-radiological findings are supplemented by histological evidence of epithelioid granulomas in more than one system. Markers of activity include elevated levels of serum angiotensin converting enzyme, abnormal calcium metabolism, positive kveim test, intrathoracic uptake of radioactive gallium and abnormal fluorescin angiography.

Future Prospects in Diagnostic Strategy

The main challenge before an oncologist is to be able to differentiate between a sarcoid like reaction that can mimic tumor recurrence/ deposits in lymph node radiologically. Nevertheless, they also have to keep in mind that neoplastic pathology and sarcoidosis can co-exist in the same patient. Hence, there is need to perform multiple biopsies or to perform multiple sections of tissue to rule out malignant deposits in event of granulomatous response in draining node. Also, the pathologist should search for cytokeratin expression or clonality keeping in mind close association between two pathologies. To differentiate between malignant and benign nodules is such a common problem encountered by radiologist that has provided the impetus to explore alternative metabolic imaging using PET so as to render accurate diagnosis without the need for unnecessary biopsies (83, 84). The diagnostic utility of such novel techniques over conventional histopathological examination is yet an unexplored area.

Conclusion

There is subtle but definite association between malignancy and benign granulomatous inflammation. There are multiple etiologies responsible for the co-existence of the two pathologies including an immunological response to tumor antigen. A close scrutiny of such nodes with granuloma is necessary to avoid underdiagnosis of metastatic disease or overstaging TNM grading in presence of nodal enlargement with mere granulomatous response. Apart from clinical challenges, the biological significance of such granulomas in inducing the remission or shielding tumor cells from host lymphocytes is also an area open for future research.

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