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Non-caseating granulomas in patients after the diagnosis of cancer: clinical characteristics and outcome

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Abstract. *Background:* The association between cancer and non-caseating granulomas is controversial. The aim of this study is to describe the clinical characteristics and outcome of a cohort of patients found to have non-caseating granulomas following the diagnosis of cancer. *Methods:* Retrospective review of medical records. *Results:* There were 30 patients with non-caseating granulomas following the diagnosis of cancer. There were 21 females and 14 patients were African Americans. Breast, lung, and head and neck cancers were the most common malignancies. The time between the diagnosis of cancer and non-caseating granulomas was a mean of 27.6 months (range 3 to 245 months). New mediastinal lymphadenopathy were present in 29 patients and pulmonary infiltrates or nodules were detected in 15 patients. All patients who underwent FDG-PET scan (n=18) had FDG avid findings with a mean SUV of 6.8 (range 2.8-19.4). Non-caseating granulomas were diagnosed by mediastinoscopy (12 patients), EBUS-FNA (6 patients), surgical thoracic biopsy (3 patients), transbronchial biopsy (2 patients), and other biopsies (7 patients). Patients were followed for a mean of 32.7 months (range 6-98 months) and 3 patients developed recurrence of the primary cancer. *Conclusion:* Non-caseating granulomas should be considered in patients with cancer who develop lymphadenopathy or pulmonary nodules. Recurrence of cancer should not always be assumed, and tissue diagnosis is essential. *(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 44-49)*

Key words: cancer, non-caseating granulomas

The development of mediastinal lymphadenopathy or new pulmonary lesions in patients with cancer usually indicates recurrence or new primary malignancy. Furthermore, diagnostic studies such as FDG-PET that reveal avid lesions are commonly taken as confirmation of cancer recurrence. However, patients with cancer are also prone to non-malignant conditions, which may be FDG avid, such as infections and sarcoidosis.

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The development of a non-caseating granulomatous or sarcoid-like reaction in patients with cancer has been described by several case reports and small case series (1-6. No definite causal relationship has been identified, however these reports suggest that there is increased frequency of ganulomatous reaction in patients with a variety of cancers. This report describes the clinical characteristics of a series of patients who were found to have non-caseating granulomas following the diagnosis of cancer and examines the clinical implications of this finding.

Methods

The study was conducted at a tertiary urban medical center that includes a comprehensive cancer

center in Detroit, Michigan. An Institutional Review Board approval was obtained to conduct this study. The pathology department records were searched from 2001 to 2010 using the key words cancer and non-caseating granulomas. A preliminary review of the medical records was conducted. Patients with history of cancer who later on underwent a tissue diagnosis of non-caseating granulomas were included in the analysis. The medical records of these patients were reviewed (by SB, RA and TDK) for demographic data, details about the cancer diagnosis, including stage and treatment. Also data related to the finding of non-caseating granulomas including microbiological studies, clinical and radiological features, method of diagnosis, treatment and follow up were collected.

Results

There were 30 patients who had history of cancer and then underwent tissue diagnosis of non-caseating granulomas. Infectious causes of granulomatous disease were excluded by negative stains and cultures for fungi and mycobacteria, clinical history and follow up. None of these patients were known to have sarcoidosis prior to the diagnosis of cancer. The clinical characteristics of these patients are summarized in Table 1. The mean age of these patients was 55.4 year (SD ± 11.7). Twenty one patients were females and 14 were African Americans. The origin of cancer was most commonly breast (10 patients), followed by nonsmall cell lung cancer and head and neck cancer (4 patients each). At the time of diagnosis, the underlying cancer was limited (stage I or II) in 18 patients and advanced (stage III or IV) in 12 patients. Twenty five patients underwent surgical resection of the primary cancer. Twenty two patients had chemotherapy and/or radiotherapy. The chemotherapy was paclitaxel based in 13 out of 16 patients.

The diagnosis of non-caseating granulomas was made a mean of 27.6 months following the diagnosis of cancer (range 3-245 months) (Table 2). In 18 and 22 of the patients, noncaseating granulomas were detected within 12 and 24 months, respectively of the diagnosis of cancer. Based on CT scan studies at the time of diagnosis of non-caseating granulomas, 29 patients had mediastinal lymphadenopathy. In 15 of these patients, there were associated pulmonary infiltrates or nodules. Six patients had additional abnormalities outside the thorax (axillary lymphadenopathy 2 patients, pelvic lymphadenopathy 2 patients, peri-gastric lymphadenopathy 1 patient, and liver nodules 1 patient). One patient with prostate cancer had pelvic lymphadenopathy with no thoracic abnormalities. Eighteen patients underwent

Table 1. The baseline characteristics of patients (n=30)

Characteristic	Value
Age- year (mean ± SD)	55.4 (± 11.7)
Female/male	21/9
Caucasian/ African American	16/14
History of smoking	17
Underlying cancer	
- Breast cancer	10
- Lung cancer	4
- Head and neck cancer	4
- Prostate cancer	3
- Others*	9
Cancer stage at diagnosis	
- Limited (stage I or II)	18
- Advanced (stage III or IV)	12
Cancer treatment	
- Surgery	25
- Chemotherapy and/or radiation	22

* Other cancers were: melanoma- 2 patients, ovarian, endometrial, cervical, seminoma, colon, appendix, and thymoma- one patient each

Table 2. The patients' characteristics at the time of diagnosis of non-caseating granulomas

Characteristic	Value
Time between diagnosis of cancer and non-caseating granulomas *(average, range in months)*	27.6 (3-245)
CT scan findings	
- Mediastinal lymphadenopathy	29
- Pulmonary infiltrates/ nodules	15
- Extrathoracic lymphadenopathy	6
FDG-PET scan (n=18)	
- FDG-avid lesions	18
- Mean maximum SUV (range)	6.8 (2.8-19.4)
Method of diagnosis of non-caseating granulomas	
- Mediastinoscopy	12
- EBUS-FNA	6
- Surgical thoracic biopsy	3
- Transbronchial biopsies	2
- CT guided lung biopsy	2
- Other lymph node or liver biopsy	5
PFT (n=20)	
- FVC (% of predicted)	89%
- FEV1(% of predicted)	85%
- FEV1/FVC	73%
- TLC (% of predicted)	89%
- Adjusted DLCO (% of predicted)	60%

FDG-PET scan for evaluation of abnormal radiological findings. All patients had high SUV, with average maximum SUV 6.8 (range 2.8-19.4). All patients underwent diagnostic procedures to exclude cancer recurrence. The tissue diagnosis of non-caseating granulomas was made by mediastinoscopy in 12 patients, transbronchial needle aspirate using endobronchial ultrasonography in 6 patients, surgical thoracic biopsy (lung biopsy and mediastinal lymph node sampling) by thoracotomy or VATS in 3 patients, bronchoscopy with transbronchial biopsies in 2 patients. Other methods of diagnosis were CT guided fine needle aspirate of lung nodule in 2 patients, abdominal or pelvic lymph node biopsies 2 patients, axillary lymph node biopsy in 2 patients, and liver biopsy in 1 patient.

The patients were followed for mean of 32.7 months (median 22, range 6-98 months) after the diagnosis of non-caseating granulomas. Four patients had other features that were suggestive of systemic sarcoidosis (pulmonary infiltrates with respiratory symptoms in 3 patients and skin lesions in 1 patient). One of these patients had an additional transbronchial lung biopsy and another had skin biopsy that revealed non-caseating granulomas. Six patients were treated with systemic corticosteroids. According to the medical records the indications for corticosteroid therapy were respiratory symptoms in 4 patients and a therapeutic trial to demonstrate resolution of the radiological findings in 2 patients.

During the follow up period, 3 patients had recurrence of the underlying malignancy documented by tissue biopsy 3-6 months following the diagnosis of non-caseating granulomas. These patients had head and neck cancer, lung cancer, and endometrial cancer. The recurrence of cancer was diagnosed by endobronchial ultrasonographic fine needle aspirate of mediastinal lymph node, mediatinoscopy, and pelvic mass fine needle aspirate, respectively. These patients died from progressive underlying malignancy an average of 19 months following the diagnosis of non-caseating granulomas.

Discussion

The development of non-caseating granulomas in patients with cancer has been described in several small series and case reports. Earlier reports suggested that 0.7-13% of patients with cancer develop histopathological evidence of non-caseating granulomas (2-4, 7). A recent study of 2048 FDG-PET/CT examinations as part of the evaluation of cancer reported that the prevalence of sarcoid-like reaction was 1.1% from review of radiological reports and 0.6% based on histological confirmation (6). Another recent review of 565 mediastinoscopies, non-caseating granulomas were found in 21 patients (3.7%) after the diagnosis of cancer (5). It is possible that these figures represent selection bias in studies from major cancer centers. There is on-going debate whether the finding of non-caseating granulomas in patients with cancer represents true sarcoidosis or a non-specific inflammatory reaction. Also whether there is an association between this reaction and the diagnosis of cancer or this is a coincidental finding. If non-caseating granulomas in patients with cancer represent sarcoidosis, it appears that its prevalence is higher than the estimated prevalence of 10 to 20 cases of sarcoidosis per 100,000 of the general population (5).

The spectrum of underlying cancers in patients who develop non-caseating granulomas is wide and includes a variety of solid tumors and lymphomas (2). Based on previous reports, higher frequency was described in patients with carcinomas of the skin, testicular cancers, and Hodgkin's lymphoma. Granulomatous reaction was extremely rare in patients with sarcomas (2). In this study, breast cancer was the most common underlying malignancy (33%), followed by lung and head and neck cancers. It appears that the development of non-caseating granulomas is not unique to certain cancers and the rate of occurrence differs from one report to another according to the frequency of cancers studied and practice patterns of obtaining tissue confirmation in patients suspected to have cancer recurrence.

The pathogenesis of non-caseating granulomas in patients with cancer remains incompletely understood. It could be related to degenerative or necrotic changes within the tumor itself (2). Also granulomas may be a local inflammatory reaction in the regional draining lymph nodes. This would explain the findings of noncaseating granulomas in mediastinal lymph nodes in patients with lung cancer and axillary lymph nodes in patients with breast cancer reported in this study. On the other hand, non-caseating granulomas in patients with cancer may be me-

diated by humoral and/or cellular immune reactions to antigens or factors secreted by cancer cells and result in remote lymphadenopathy or systemic disease involving multiple organs (2-4, 8). Some of the patients in this study had remote lymphadenopathy and were associated with symptoms that required corticosteroid therapy. Tumor necrosis factor (TNF)-alpha, which plays a role in the initiation, proliferation, angiogenesis and metastasis of a variety of cancers has also been described to play a role in the pathogenesis or non-caseating granulomas in sarcoidosis and other granulomatous diseases (9, 10). So it is possible that TNF-alpha associated with the underlying malignancy may trigger the development of non-caseating granulomas in these patients. There are also reports that suggest that certain chemotherapeutic agents predispose to hypersensitivity reaction in the form of non-caseating granulomas. These agents include alpha interferon, IL-2, cisplatin, and bleomycin (2, 11, 12). In this study, 13 out of 16 patients who received chemotherapy, the regimen was paclitaxel based. However, only 53% received chemotherapy, so it unlikely that chemotherapy alone explains the development of non-caseating granulomas in patients with cancer. There are also reports that suggest that granulomatous reaction in patients with cancer represents an immune host defense mechanism against the spread of tumor. This is supported by reports of better prognosis in patients with Hodgkin's lymphoma and gastric cancer who were found to have non-caseating granulomas (13-15). In this study, after a fairly long follow up, cancer recurrence was documented in only 3 patients after the diagnosis of non-caseating granulomas. Prospective trials or case control studies are needed to address whether cancer patients who develop non-caseating granulomas have better prognosis.

There is ongoing controversy whether the finding of non-caseating granulomas in patients following the diagnosis of cancer represents sarcoidosis. The patients with non-caseating granulomas following cancer have clinical features that are similar and others that are different from classic sarcoidosis in the general population. The age of the patients in this study at the time of diagnosis of non-caseating granulomas was an average of 55 years, which is similar to what was described in previous reports (5, 6). This age is older than what is expected for sarcoidosis in the general population (usually 20-39 years) (16). This is probably reflective of the fact that these patients were diagnosed with non-caseating granulomas after the developing solid cancers, which are more common in older age. Seventy percent of patients were females. This is similar to the higher incidence of sarcoidosis in women (16). On the other hand, this finding may be due to the fact that 43% patients in this series had women related malignancies. The reported race is African American in 47% of patients in this study. This is probably due to the urban location of the Medical Center and the fact that it serves a large African American population. On the other hand, it is known that sarcoidosis is more prevalent in African American population. The relatively high frequency of African American patients in this study raises the possibility that some of these patients may have had sarcoidosis prior to the diagnosis of cancer. However, the older age, the lack of other systemic features of sarcoidosis, and the new findings that triggered diagnostic procedures in these patients make this theory less likely. Multicenter studies are necessary to address whether the diagnosis of non-caseating granulomas following cancer is more common in African American patients.

The majority of patients with non-caseating granulomas following cancer do not have symptoms related to this finding. Other features to suggest sarcoidosis such as arthritis, skin lesions, or ophthalmic involvement are extremely rare. Most of the patients do not require treatment with systemic corticosteroids. In this study, 20% of patients were treated with systemic corticosteroids. It is difficult from this retrospective analysis to determine whether the patients' symptoms (usually dyspnea) were related to the finding of non-caseating granulomas or other factors. The observation that most of patients do not have symptoms related to the findings of non-caseating granulomas on tissue biopsy, do not have other features typical of sarcoidosis, and do not require treatment suggests that is a unique inflammatory reaction following cancer rather than true sarcoidosis. This coincides with previous reports that describe this phenomenon as sarcoid-like reactions, or sarcoid-tissue reactions, or sarcoid-like granulomas (17).

Sixty percent of patients in this study underwent FDG-PET scans for re-staging of cancer. All these patients had FDG avid lesions. The maximum SUV in some of these cases reached 19.4. It has been

well documented that FDG avid lesions could represent benign lesions. A study of 137 patients with sarcoidosis showed that FDG PET was positive in 74% of patients (18). In another study of patients with suspected or confirmed sarcoid-like reaction, the maximum SUV was 7.3 (range 3.1-13.6) (6). These observations raise an important point that FDG avid lesions in patients with cancer should not be automatically assumed to represent cancer recurrence, rather should trigger further evaluation by tissue diagnosis unless there is overwhelming evidence of tumor recurrence. Recent development of less invasive diagnostic procedures, such endobronchial ultrasonography and navigational bronchoscopy, may make it easier to obtain tissue from these new lesions.

In this study, 97% of the patients had mediastinal lymphadenopathy. The diagnosis of non-caseating granulomas was made by mediastinoscopy in 40% patients. This procedure allows adequate sampling of lymph nodes, however it is invasive, requires general anesthesia and has limitation in reaching left mediastinal lymph nodes. The introduction of endobronchial ultrasonography with fine needle aspirate (EBUS-FNA) allows for safe, less invasive and broader reach of mediastinal lymphadenopathy. This technology was introduced to our practice in the last 2 years of the study and during this period 6 patients with cancer were diagnosed with non-caseating granulomas using this procedure. The utility of EBUS-FNA in the diagnosis of granulomatous diseases, such as sarcoidosis, was been reported previously (19, 20). Another recent study of EBUS-FNA at a cancer center identified noncaseating granulomas in 5.2% of patients with mediastinal lymphadenopathy mimicking cancer recurrence (4). In patients with cancer and FDG avid mediastinal lymphadenopathy on staging or re-staging of the underlying malignancy, we suggest proceeding with EBUS-FNA when available as the initial diagnostic procedure. This procedure is useful in confirming cancer involvement and excluding other etiologies such as non-caseating granulomas, which may change the management of these patients. The main concern with EBUS-FNA is the sampling error associated with fine needle aspirates that may miss coexisting metastatic tumor in the same lesion, as has been previously described (21, 22). In these patients, sound clinical judgment and close surveillance are warranted. If the pre-test clinical probability of tumor recurrence was high, further evaluation including mediastinoscopy may be necessary. On the other hand, EBUS-FNA may under diagnose noncaseating granulomas since this procedure does not currently allow for core biopsy of lymph nodes.

To our knowledge, this is the largest case series that provides details of the clinical characteristics of cancer patients who were later on found to have non-caseating granulomas. The report has limitations including the retrospective nature of the analysis, a single center experience, and the potential for selection bias. Further prospective multicenter studies are necessary to confirm the relationship between cancer and non-caseating granulomas, whether this reaction represents true sarcoidosis, and determine the prognostic value of this finding. Furthermore, this report illustrates the importance of tissue diagnosis in cancer patients who develop new findings, holding true to the phrase: tissue is the issue.

References

1. Brincker H, Wilbek E. The incidence of malignant tumors in patients with respiratory sarcoidosis. Br J Cancer 1974; 29: 247-51.
2. Brincker H. Sarcoid reactions in malignant tumors. Cancer Treat Rev 1986; 13: 147-56.
3. Shigemitsu H. Is sarcoidosis frequent in patients with cancer? Curr Opin Pulm Med 2008; 14: 478-80.
4. Kennedy MP, Jimenez CA, Mhatre AD, Morice RC, Eapen GA. Clinical implications of granulomatous inflammation detected by endobronchial ultrasound transbronchial needle aspiration in patients with suspected cancer recurrence in the mediastinum. J Cardiothorac Surg 2008; 25: 3-8.
5. Hunt BM, Vallières E, Buduhan G, Aye R, Louie B. Sarcoidosis as a benign cause of lymphadenopathy in cancer patients. Am J Surg 2009; 197: 629-32.
6. Chowdhury FU, Sheerin F, Bradley KM, Gleeson FV. Sarcoid-like reaction to malignancy on whole-body integrated (18)F-FDG PET/CT: prevalence and disease pattern. Clin Radiol 2009; 64: 675-81.
7. Llombart A Jr, Escudero JM. The incidence and significance of epithelioid and sarcoid-like cellular reaction in the stromata of malignant tumors. A morphological and experimental study. Eur J Cancer 1970; 6: 545-51.
8. Tangen JM, Naess A, Aasen T, Morild I. Non-caseating granulomas in patients with hematologic malignancies. A report of three cases. Acta Med Scand 1988; 223: 83-7.
9. Sethi G, Sung B, Kunnumakkara AB, Aggarwal BB. Targeting TNF for Treatment of Cancer and Autoimmunity. Adv Exp Med Biol 2009; 647: 37-51.
10. Daïen CI, Monnier A, Claudepierre P, et al. Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases. Rheumatology (Oxford) 2009; 48: 883-6.
11. Hurst EA, Mauro T. Sarcoidosis associated with pegylated interferon alfa and ribavirin treatment for chronic hepatitis C: a case report and review of the literature. Arch Dermatol 2005; 141: 865-8.

12. Logan TF, Bensadoun ES. Increased disease activity in a patient with sarcoidosis after high dose interleukin 2 treatment for metastatic renal cancer. Thorax 2005; 60: 610-1.
13. O'Connell MJ, Schimpff SC, Kirschner RH, Abt AB, Wiernik PH. Epithelioid granulomas in Hodgkin disease. A favorable prognostic sign? JAMA 1975; 233: 886-9.
14. Sacks EL, Donaldson SS, Gordon J, Dorfman RF. Epithelioid granulomas associated with Hodgkin's disease: clinical correlations in 55 previously untreated patients. Cancer 1978; 41: 562-7.
15. Pick AI, Duer D, Kessler H, Kenan Z, Weiss H, Topilski M. Delayed hypersensitivity and lymphocytic transformation in patients with Hodgkin's disease and granulomas. Cancer 1978; 41: 2192-6.
16. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-65.
17. Brincker H. The sarcoidosis-lymphoma syndrome. Br J Cancer 1986; 54: 467-73.
18. Teirstein AS, Machac J, Almeida O, Lu P, Padilla ML, Iannuzzi MC. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. Chest 2007; 132: 1949-53.
19. Tournoy KG, Bolly A, Aerts JG, et al. The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis. Eur Respir J 2009; Nov 6 [Epub ahead of print].
20. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest 2007; 132: 1298-304.
21. Brincker H. Coexistence of sarcoidosis and malignant disease: causality or coincidence? Sarcoidosis 1989; 6: 31-43.
22. Steinfort DP, Irving LB. Sarcoidal reactions in regional lymph nodes of patients with non-small cell lung cancer: incidence and implications for minimally invasive staging with endobronchial ultrasound. Lung Cancer 2009; 66: 305-8.