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Sarcoid Reactions after Chemotherapy for Hodgkin's Lymphoma

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Abstract

Introduction: There is a reported association between sarcoidosis and malignancy. This is particularly true for lymphomas and is known as the sarcoidosis-lymphoma syndrome.

Case report: A 49 year old Caucasian female presented with mediastinal and axillary lymphadenopathy. An excisional axillary lymph node biopsy showed classical Hodgkin's lymphoma, nodular sclerosis subtype. She received six cycles of conventional chemotherapy achieving a complete remission with no evidence of any lymphadenopathy on restaging imaging. However, one month after completion of chemotherapy, she developed new onset of progressive mediastinal lymphadenopathy. A mediastinoscopy and biopsy was performed showing noncaseating granulomata and the patient was diagnosed with a sarcoid reaction.

Conclusion: Sarcoidosis and sarcoid reactions must be considered in the differential diagnosis when assessing patients with persistent or enlarging masses after chemotherapy treatment for Hodgkin's lymphoma, especially since this is associated with a better prognosis. A tissue biopsy is essential prior to starting chemotherapy for presumed relapsed malignancy or persistent disease so as to avoid inappropriate treatment.

Keywords: sarcoidosis, sarcoid reactions, Hodgkin's lymphoma, malignancy

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Introduction

Brincker was the first to show a significantly higher than expected association between sarcoidosis and lymphoma of all types; an approximately 11.5 fold increased risk.¹ Lymphoma developing 1 to 2 years after the diagnosis of sarcoidosis is known as the sarcoidosis-lymphoma syndrome.¹ This syndrome has been expanded to include patients with sarcoidosis who develop other hematologic malignancies and solid tumors such as lung and liver cancer and may be better known as the sarcoidosis-malignancy syndrome.² In addition, this syndrome includes a subset of patients with hematologic malignancies and solid tumors who later develop sarcoidosis.² Paraneoplastic sarcoidosis develops concurrently with or within a year of the diagnosis of hematologic malignancy or solid tumor.²

Noncaseating granulomata of the regional lymph nodes or the organ of tumor involvement, without the systemic manifestations of sarcoidosis, are known as sarcoid reactions.² As shown in this case report, sarcoidosis and sarcoid reactions must be excluded by a tissue biopsy when assessing patients with persistent or enlarging masses after chemotherapy administration for malignancies so as to avoid inappropriate treatment.

Case Report

A 49 year old woman developed pruritus and progressive axillary lymphadenopathy. Computed tomography (CT) and [¹⁸F] fluorodeoxyglucose-positron emission tomography (FDG PET) showed enlarged, FDG avid lymph nodes in the left supraclavicular, left axillary and mediastinal regions. An excisional left axillary lymph node biopsy was performed which showed classical Hodgkin's lymphoma, nodular sclerosis subtype. Neoplastic Reed-Sternberg cells were positive for CD30 and CD15 but negative for CD20 and CD3. A bone marrow biopsy was normocellular without evidence of Hodgkin's lymphoma. Stage IIA Hodgkin's lymphoma was diagnosed. Six cycles of doxorubicin, bleomycin, vinblastine, dacarbazine chemotherapy were initiated. After the fourth cycle of chemotherapy, a PET/CT scan showed no further FDG avidity or any evidence of lymphadenopathy. The patient achieved a complete remission. PET/CT performed one month after completion of chemotherapy, showed new hilar and mediastinal

lymphadenopathy with associated FDG avidity. There were no lung parenchymal abnormalities. A mediastinoscopy with biopsy was performed. The lymph node biopsy showed the lymph node to be entirely replaced by confluent noncaseating epithelioid granulomata with focal necrosis on hematoxylin and eosin (H&E) stain. No neoplastic Reed-Sternberg cells were noted. Gomori Methanamine Silver (GMS) and acid fast bacilli (AFB) stains were negative for fungal or mycobacterial organisms. Three months after completion of chemotherapy, another PET/CT continued to show stable mediastinal and hilar lymphadenopathy with associated FDG avidity in these areas. Lymph nodes were less than 2 centimeters in largest diameter. The patient was asymptomatic without constitutional symptoms. Physical exam revealed no peripheral lymphadenopathy or hepatosplenomegaly. The angiotensin converting enzyme (ACE), lactate dehydrogenase, beta 2 microglobulin, liver function, renal function, and calcium were normal. A complete blood count was remarkable only for lymphopenia. Human immunodeficiency virus (HIV) testing was negative. A second mediastinoscopy and biopsy again showed confluent noncaseating granulomata of the lymph node suggestive of a sarcoid reaction (Figs. 1 and 2). GMS and AFB stains were negative for fungi and acid fast bacilli. There was no evidence of Hodgkin's lymphoma on routine histology. Immunohistochemistry staining for (cluster of differentiation) CD30 and CD15 suggestive of neoplastic Reed-Sternberg cells was absent. Flow cytometry of the lymph nodes was unremarkable. A bone marrow biopsy showed

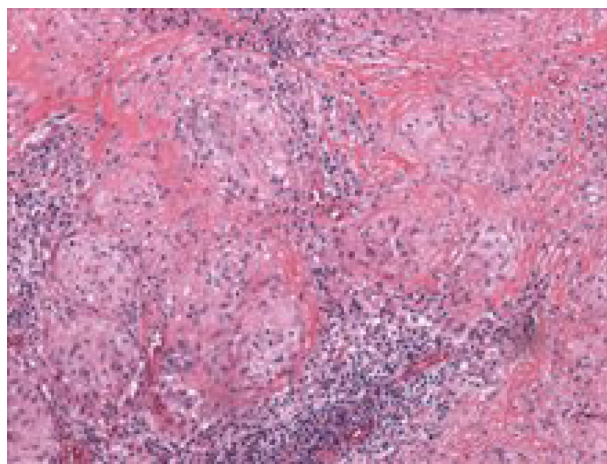


Figure 1. Mediastinal lymph node (H&E, 200×) showing confluent noncaseating granulomata.

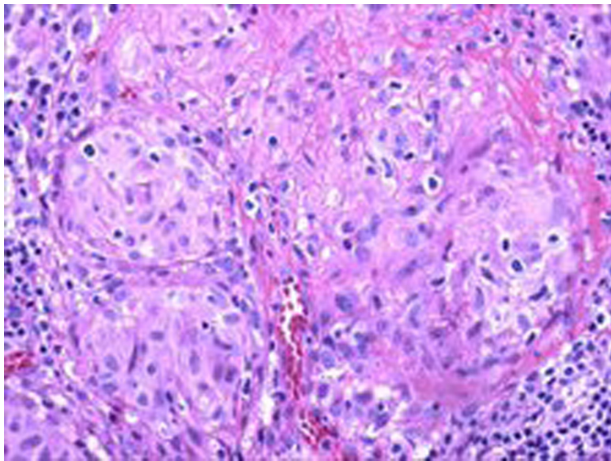


Figure 2. Mediastinal lymph node (H&E, 400×) showing noncaseating granulomata.

no Hodgkin's lymphoma or significant pathologic change. Two years after completion of chemotherapy the patient remained asymptomatic with persistent but stable mediastinal and hilar lymphadenopathy on PET/CT and no evidence of relapsed Hodgkin's lymphoma or systemic manifestations of sarcoidosis.

Discussion

The relationship between sarcoidosis and malignancy is a controversial subject. The increased incidence of malignancy in patients with sarcoidosis was first described by Brincker.¹ Between 1962 and 1972, 48 out of 2544 patients enrolled in the Danish sarcoidosis registry developed malignant tumors including lymphoid and solid tumors compared to only 33 malignant tumors on the basis of age and gender specific incidences in the control group.¹ Lymphomas developed in 17 patients; 8 with Hodgkin's lymphoma, 9 with non-Hodgkin's lymphoma, chronic lymphocytic leukemia or multiple myeloma. Patients with chronic active sarcoidosis had an 11.5 fold increased incidence of lymphoma.¹ The same authors, after a review of a cohort of 18% of the Danish population, estimated the incidence of lymphoma of all types in patients with sarcoid to be 5.5 fold higher than expected.³ The only other malignancy occurring with higher frequency in the same population was lung cancer which had a 3.5 fold higher incidence in patients with sarcoid than in the general population.³ Brincker postulated the existence of a sarcoidosis-lymphoma syndrome characterized by the development of a lymphoid neoplasm one

to two years after a diagnosis of sarcoidosis. These patients also had a median age of onset of sarcoidosis of more than 40 years which is at least 10 years older than that of unselected patients with sarcoidosis. Hodgkin's lymphoma was found to occur more frequently than other types of lymphoma.² Hodgkin's and non-Hodgkin's lymphoma occurred earlier than chronic lymphocytic leukemia and paraproteinemias, probably reflecting the differing natural history of these conditions.³ In another sarcoid registry study, Reich found no instances of sarcoidosis accompanying Hodgkin's lymphoma using the linkage criteria previously reported (associated malignancy occurring 1 to 2 years after the diagnosis of sarcoidosis and with a median age of onset of sarcoidosis at least 10 years older than that of unselected patients with sarcoidosis).⁴ However, more recently, in the largest study to be conducted on this topic, involving 10,037 patients hospitalized for sarcoidosis in Sweden between 1964 and 2004, there was an overall 40% excess incidence of cancer and the risk was still above unity (1.18) when analyzing only those cancers diagnosed after one year of follow up.⁵ Squamous cell carcinomas of the skin, non-Hodgkin's lymphoma and leukemias accounted for the majority of the cancers.

Sarcoidosis is known to be associated with activation of CD4⁺ T cells and down regulation of CD8⁺ T cells leading to dysfunction in the immunoregulatory pathways and the formation of noncaseating granulomata and lymphoid neoplasms.⁶ Sarcoidosis and Hodgkin's disease have several immunologic similarities; both are characterized by cutaneous anergy, peripheral lymphopenia, and prominent tissue infiltration of helper T cells. Another theory, postulates that clinical sarcoid is a generalized cell mediated immune response to tumor antigens representing the systemic counterpart of the localized noncaseating granulomata present within tumors.^{2,6} In addition to the possible mechanisms already discussed, immunosuppression from chemotherapy or drug reaction are other possibilities.² For example, bleomycin concentrates more in the lymph nodes, skin and lung tissue than other agents and these are the tissues with a predilection for developing sarcoidosis.^{2,6} However sarcoidosis can occur after malignancy without the administration of chemotherapy.¹⁰

Usually sarcoidosis precedes the development of lymphomas.⁷ On occasion, lymphoma can also



predate the development of sarcoidosis.⁸ For example, Suen et al analyzed 6 cases of patients with biopsy proven malignancy (ovarian cancer, breast cancer, Hodgkin's disease, non-Hodgkin's lymphoma and T cell lymphoma) who developed biopsy proven sarcoidosis on average 9 months after the onset of malignancy with or without the prior administration of chemotherapy.¹⁰ The sarcoidosis-lymphoma syndrome has been expanded to include the diagnosis of other hematological malignancies and solid tumors occurring one to two years after or before the diagnosis of sarcoidosis and may be better known as the sarcoidosis-malignancy syndrome.² The diagnosis of sarcoidosis concurrently with or within one year of the diagnosis of cancer is known as paraneoplastic sarcoidosis.²

The diagnosis of sarcoidosis, a multisystem granulomatous disorder of unknown etiology, is based on a combination of clinical, radiological and histological findings.¹¹ The PET scan shows FDG avidity in lymph nodes involved by sarcoidosis indicative of immune activation and resultant metabolic activity.¹² Features supporting a diagnosis of sarcoidosis include clinical findings (fever, cough, dyspnea, parotid gland enlargement, arthralgias, arthritis, peripheral lymphadenopathy, cranial nerve palsies, meningitis), biochemical tests (such as hypercalcemia and lymphopenia) and findings of noncaseating granulomata on tissue biopsy.¹¹ Infections need to be excluded, in particular mycobacterial and fungal infections, as these can morphologically and clinically mimic sarcoidosis.¹¹ The angiotensin converting enzyme (ACE) level is elevated in only two thirds of cases of sarcoidosis. The Kveim-Siltzbach test, which is positive in 70% of cases of sarcoidosis, is no longer in general use and has been supplanted by transbronchial biopsy and mediastinoscopy with lymph node biopsy.¹¹ The histologic hallmark of sarcoidosis, noncaseating granulomata, can be seen in regional draining lymph nodes or the organ of tumor involvement and are referred to as sarcoid reactions in patients who do not have all the criteria for systemic sarcoidosis.¹³ Sarcoid reactions can occur in 4.4% of carcinomas, 13.8% of Hodgkin's lymphoma and 7.3% of non-Hodgkin's lymphomas.¹³ These local sarcoid reactions can generalize over time leading to difficulty in diagnosing tumor related sarcoid reactions versus systemic sarcoidosis. The presumed mechanism for the formation of sarcoid

reactions is an induced T cell mediated host response to soluble tumor antigens shed by the tumor cells or released during tumor necrosis.¹⁴ Sarcoid reactions are a positive prognostic indicator in patients with Hodgkin's disease as well as gastric cancer as these patients have a longer relapse free survival and overall survival.^{2,14}

In this article, the patient with Hodgkin's lymphoma had new onset of progressive mediastinal and hilar lymphadenopathy after achieving a complete response with chemotherapy. The mediastinal lymph node biopsies, repeated on two occasions, 1 month and 3 months after completion of chemotherapy, showed confluent noncaseating granulomata without evidence of neoplastic Reed-Sternberg cells to suggest relapsed Hodgkin's lymphoma. There was also no evidence of mycobacterial or fungal infection. The patient had no constitutional symptoms. This patient was diagnosed with a sarcoid reaction. The patient has been followed for 2 years after completion of chemotherapy with stable but persistent mediastinal and hilar lymphadenopathy and without recurrence of Hodgkin's lymphoma or manifestations of systemic sarcoidosis.

The differential diagnosis of a persistent or enlarging mass after chemotherapy treatment for Hodgkin's lymphoma includes fibrosis, thymic hyperplasia and persistent or relapsed lymphoma. To this list must be added sarcoidosis and sarcoid reactions, as highlighted by this article. There should be an awareness of the possibility of sarcoid reactions in the setting of a persistent or enlarging mass after chemotherapy, especially since these are associated with a better prognosis. A tissue biopsy is essential prior to starting chemotherapy for a presumed relapse or treatment failure in patients with Hodgkin lymphoma so as to avoid inappropriate therapy.

Author Contributions

BW analyzed and interpreted the patient data and wrote the article.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author



confirms that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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