Chapter

# Sarcoid Granulomas in Malignancy

*Komal Arora, Neeraj Kaur and Jae Y. Ro*

## Abstract

Noncaseating epithelioid granulomas without accompanying systemic symptoms of sarcoidosis have been described in association with many primary tumors where they are designated as sarcoid-like (SL) reaction. Morphologically, this SL reaction is similar to granulomas found in systemic sarcoidosis comprising of focal accumulation of epithelioid cells and multinucleated giant cells. They can be seen either adjacent to the primary malignancy or in local draining lymph nodes. Additionally, sarcoid-like granulomas can affect other organs distant from the primary neoplasm, such as the spleen, bone marrow, and skin. This sarcoid-like reaction is thought to occur as an immunologic T-cell-mediated response to antigens expressed by the neoplastic cells or soluble tumor antigens. Whether the presence of this sarcoid-like reaction has any prognostic significance in the associated neoplasm is unclear.

**Keywords:** sarcoid-like granulomas, malignancy, prognosis

## 1. Introduction

Granulomatous inflammation is a type of chronic tissue reaction characterized histologically by accumulation of epithelioid cells and multinucleated giant cells. Sarcoidosis is a systemic granulomatous disorder of unknown etiology that affects various organs. Sarcoid-like (SL) granulomas/reactions can be seen in patients with malignant tumors without the history of systemic sarcoidosis. These reactions were first described by Wolbach in 1911 [1]. Subsequently, Herxheimer in 1917 reported sarcoidal granulomas in patients with carcinomas of breast, rectum, and cystic duct [2]. These granulomas can occur either within the primary tumor, adjacent to the primary malignancy, in local draining lymph nodes, or in organs distant from the primary malignancy such as the spleen, bone marrow, and skin. This SL reaction is thought to occur in response to antigens expressed by the neoplastic cell or soluble tumor antigens that trigger a T-cell-mediated local immune response. Other etiologies of granuloma formation in patients with malignancy are co-existing sarcoidosis, infectious etiology, and reaction to therapeutic drug or procedure. The SL granulomas have been reported to occur with an average frequency of 14% in Hodgkin lymphoma cases, 7% in non-Hodgkin lymphomas, 50% in seminomas, less than 1% in sarcomas, and 4% in various carcinomas [3, 4].

## 2. Histologic features

Morphologically, the granulomas of SL reaction are similar to those seen in sarcoidosis. The granulomas are comprised of central focus of epithelioid cells surrounded by a rim of lymphocytes. Both Langhans-type and foreign body-type giant cells containing asteroid body and Schaumann body inclusions have been reported [5, 6]. Usually, these granulomas are noncaseating with no central necrosis. In solid tumors such as renal cell carcinomas, the granulomas have been described in intratumoral and peritumoral location as well as in the nonneoplastic kidney and draining lymph nodes [7].

## 3. Pathophysiology

The granuloma formation in sarcoidosis is mediated by T-cells [8]. The granulomas in SL reactions are postulated to be a T-cell-mediated immunologic reaction to soluble tumor antigens shed by the tumor cells or released during tumor necrosis [3, 9]. In the study by Kurata et al., the authors found that the solitary granulomas in SL reactions first occur between lymph sinus and T-zone, the multiple granulomas mainly occur within T-zone, and the confluent types often occupy the whole lymph node except some residual lymphoid follicles [10]. Such a pattern suggested that the granulomas grow along the T-zone, where antigen presentation mainly occurs. Recently, some authors have also hypothesized that dendritic cells play an important role in the mechanism of T-cell activation that leads to formation of granulomas [10, 11].

SL reactions have also been reported after interferon therapy in patients with malignant melanoma and after interleukin-2 therapy for renal cell carcinoma [12, 13].

## 4. Prognostic significance

A dense lymphocytic infiltrate at the margins of some malignant tumors such as medullary carcinoma of the breast and colonic adenocarcinoma has been associated with an improved prognosis. This improved prognosis has been attributed to an immune-mediated cytotoxic T cell response to the tumor. Similarly, the SL reactions, which are thought to be an immune response to the tumor antigens, are expected to be associated with improved prognosis.

Currently, the prognostic significance of these SL granulomas is debatable. Some authors hypothesized that SL granulomatous reactions could play an important role in the host's defense against metastatic spread [9, 14]. Several studies have shown that the presence of granulomas in Hodgkin's disease correlated with improved survival in all stages of disease [15–17]. Similarly, SL reactions in gastric carcinoma have been reported to have a good prognosis [18]. Takeuchi et al. demonstrated that the incidence of SL reactions in the regional lymph nodes decreased as gastric cancer progressed [19]. In another study on seven cases of gastric cancer associated with SL reaction, none of the patients had any episodes of recurrence, suggesting a more favorable prognosis when compared with gastric cancer patients without a SL reaction [20].

SL reactions are relatively less common in solid tumors as compared to lymphomas. In a study by Lynch et al., the authors found that SL reaction was associated with improved prognosis in small cell carcinoma of the lung [21]. Recently, Steinfort et al. [22] studied eight patients with nonsmall cell carcinoma lung where sarcoidal granulomas were present in regional lymph nodes. The authors concluded that the

presence of sarcoidal reactions within regional lymph nodes of these patients predicted a lower rate of disease recurrence after definitive surgical resection. However, an earlier study by Kamiyoshihara et al. ruled out this hypothesis in lung cancer and found the SL reactions to be of no prognostic significance [23]. Similarly Tomimaru et al. studied 22 lung carcinoma patients with SL reaction in the regional lymph nodes and found no statistically significant difference in the overall survival [24].

Few cases of breast carcinoma and colorectal carcinoma associated with a stromal granulomatous SL reaction have been reported in the literature [25–30]. The authors were not able to make a definitive comment on the prognostic significance of these SL reactions in these published reports due to limited number of cases.

Recently, we published the largest case series on SL reactions in renal cell carcinoma [7]. However, due to the limited follow-up and small number of cases, we could not conclude if these SL granulomas had any prognostic significance in renal cell carcinomas. We hypothesized that the high content of glycogen and lipid in tumor cells of clear cell and clear cell papillary renal cell carcinomas possibly triggered a granulomatous reaction, similar to that seen in seminomas.

In a recent case series published by Lashari et al., the authors reported the occurrence of granulomatous mediastinal lymphadenitis at a site remote from the location of primary gynecological malignancy without evidence of metastatic disease [31].

## 5. Sarcoidosis coexisting with malignancy

Sarcoidosis is associated with an increased risk for cancer development in various organs such as lung, liver, or stomach [32, 33]. Many hematologic malignancies and melanomas have also been associated with sarcoidosis. Coexistence of sarcoidosis and cancer has been associated with a diminished survival rate [34]. Sarcoidosis can present in patients before, during, or after diagnosis of malignancy [35, 36].

The association between systemic sarcoidosis and malignant lymphoma was first described by Brincker in 1986. The author used the term "Sarcoidosis-lymphoma syndrome" to describe this association [37]. It refers to development of lymphoma and other hematological malignancies after diagnosis of sarcoidosis as well as includes patients with lymphoma and hematological malignancies who subsequently develop sarcoidosis [35]. Differentiating between granulomas of systemic sarcoidosis and SL granulomas in patients with malignancy is difficult based on morphology alone. Diagnosis of systemic sarcoidosis is made in the presence of additional well-recognized clinical and radiological findings.

## 6. Diagnostic dilemmas

Radiologically, a SL reaction can mimic tumor recurrence/deposits in the draining lymph nodes. Hence, differentiating lymphadenopathy caused by a SL reaction and metastatic disease is very important clinically. Definitive diagnosis can be made only by histopathological examination of the lymph nodes.

Granulomas in the draining lymph nodes of malignancy can be both infectious as well as SL reaction. The center of these granulomas may sometimes have nests or isolated tumor cells. Hence, a close scrutiny of such granulomas should be performed to avoid missing metastatic disease. Immunostaining with cytokeratin may be required for recognizing these in difficult cases [38].

Knowledge of the usual tumor behavior along with correlating radiologic and histologic findings is important to avoid misdiagnosis.

## Author details

Komal Arora[1], Neeraj Kaur[2] and Jae Y. Ro[3]*

1 University of Pittsburgh Medical Center Horizon Hospital, Farrell, PA, United States

2 University of Texas Health Science Center, San Antonio, TX, United States

3 Houston Methodist Hospital, United States

*Address all correspondence to: jaero@houstonmetodist.org

## References

[1] Wolbach SB. A new type of cell inclusion, not parasitic, associated with disseminated granulomatous lesions. Journal of Medical Research. 1911;**24**(2):243-258

[2] Herxheimer G. Uber karzinoma und tuberkulose. Zeitschrift für Tuberkulose. 1917;**27**:251-258

[3] Brincker H. Sarcoid reactions in malignant tumours. Cancer Treatment Reviews. 1986;**13**:147-156

[4] Khurana KK, Stanley MW, Powers CN, Pitman MB. Aspiration cytology of malignant neoplasms associated with granulomas and granuloma-like features: Diagnostic dilemmas. Cancer. 1998;**84**(2):84-91

[5] Nadel EM, Ackerman LV. Lesions resembling Boeck's sarcoid in lymph nodes draining an area containing a malignant neoplasm. American Journal of Clinical Pathology. 1950;**20**(10):952-957

[6] Symmers WS. Localized Tuberculoid granulomas associated with carcinoma: Their relationship to Sarcoidosis. The American Journal of Pathology. 1951;**27**(3):493-521

[7] Arora K, Divatia MK, Truong L, Shen SS, Ayala AG, Ro JY. Sarcoid-like granulomas in renal cell carcinoma: The Houston Methodist hospital experience. Annals of Diagnostic Pathology. 2017c;**31**:62-65

[8] Crystal RG, Hunninghake GW, Gadek JE, Keogh BA, Rennard SI, Bitterman PB. The pathogenesis of sarcoidosis. In: Chretien J, Marsac J, Saltiel JC, editors. Sarcoidosis and Other Granulomatous Disorders. Paris: Pergamon Press; 1981. pp. 13-35

[9] Bässler R, Birke F. Histopathology of tumour associated sarcoid-like stromal reaction in breast cancer. An analysis of 5 cases with immunohistochemical investigations. Virchows Archiv. A, Pathological Anatomy and Histopathology. 1988;**412**(3):231-239

[10] Kurata A, Terado Y, Schulz A, Fujioka Y, Franke FE. Inflammatory cells in the formation of tumor-related sarcoid reactions. Human Pathology. 2005;**36**(5):546-554

[11] Ota M, Amakawa R, Uehira K, Ito T, Yagi Y, Oshiro A, et al. Involvement of dendritic cells in sarcoidosis. Thorax. 2004;**59**:408-413

[12] Massaguer S, Sánchez M, Castel T. Mediastinal sarcoidosis induced by high-dose alpha-2-interferon therapy in a patient with malignant melanoma. European Radiology. 2004;**14**:1716-1717

[13] 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**:610-611

[14] Pavic M, Debourdeau P, Vacelet V, Rousset H. Sarcoidosis and sarcoid reactions in cancer. La Revue de Médecine Interne. 2008;**29**:39-45

[15] O'Connell MT, Schimpff SC, Kirchner RH, Aht AR, Vicrnik PH: Epithelioid granulomas in Hodgkin disease. A l·avorable prognostic sign? Journal of the American Medical Association. 1975;**233**:886-889

[16] 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**(2):562-567

[17] Brincker H. Sarcoid reactions and sarcoidosis in Hodgkin's disease and

other malignant lymphomata. British Journal of Cancer. 1972;**26**(2):120-123

[18] Nakamura M, Mizuta E, Morioka H, Nakamura M, Isiglo K. Multiple early gastric cancer associated with sarcoid-like reaction in the regional lymph nodes. Journal of Gastroenterology. 2001;**36**(10):710-717

[19] Takeuchi H, Suchi T, Suzuki R, Sato T. Histological study of immune parameters of regional lymph nodes of gastric cancer patients. GANN Japanese Journal of Cancer Research. 1982;**73**:420-428

[20] Yamamoto T, Tateishi H, Nishimura Y, Watanabe M, Ukyo S, Miyake T, et al. A study of gastric cancer with sarcoid reaction as observed in the regional lymph node. Nippon Syokakibyo Gakkai Zasshi (Japanese Journal of Gastroenterology). 1980;**77**:1555-1561

[21] Lynch JP 3rd, Flint A, Miller DM, Fantone JC. Noncaseating pulmonary granulomas associated with small cell carcinoma of the lung. The American Journal of Medicine. 1985;**78**:691-696

[22] Steinfort DP, Tsui A, Grieve J, Hibbs ML, Anderson GP, Irving LB. Sarcoidal reactions in regional lymph nodes of patients with early stage non-small cell lung cancer predict improved disease-free survival: A pilot case-control study. Human Pathology. 2012;**43**(3):333-338

[23] Kamiyoshihara M, Hirai T, Kawashima O, Ishikawa S, Morishita Y. Sarcoid reactions in primary pulmonary carcinoma: Report of seven cases. Oncology Reports. 1998;**5**:177-180

[24] Tomimaru Y, Higashiyama M, Okami J, et al. Surgical results of lung cancer with sarcoid reaction in regional lymph nodes. Japanese Journal of Clinical Oncology. 2007;**37**:90-95

[25] Oberman HA. Invasive carcinoma of the breast with granulomatous response. American Journal of Clinical Pathology. 1987;**88**:718-721

[26] Coyne J, Haboubi NY. Micro-invasive breast carcinoma with granulomatous stromal response. Histopathology. 1992;**20**:184-185

[27] Coyne JD. Colonic carcinoma with granulomatous (sarcoid) reaction. Journal of Clinical Pathology. 2002;**55**:708-709

[28] Fujii T, Tabe Y, Yajima R, et al. Adenocarcinoma of ascending Colon associated with Sarcoid reaction in regional lymph nodes. Case Reports in Gastroenterology. 2010;**4**:118-123

[29] Nozoe T, Matsumata T, Sugimachi K. Carcinoma in villous adenoma of ascending colon associated with sarcoid reaction in the regional lymph nodes. Journal of Clinical Gastroenterology. 1999;**28**:377-379

[30] Shima T, Tanaka Y, Katsuragi K, Fujio N, Nakatani S, Kobayashi Y, et al. Sarcoid reaction in the spleen after sigmoid colon cancer resection: A case report. Surgical Case Reports. 2016;**2**(1):115

[31] Lashari BH, Asai M, Randleman G, Sack M, Patel R. Sarcoid-like mediastinal lymphadenopathy in gynecologic malignancy. Pulmonary Medicine. 14 February 2018;**2018**:5141575. DOI: 10.1155/2018/5141575. eCollection 2018

[32] Spiekermann C, Kuhlencord M, Huss S, Rudack C, Weiss D. Coexistence of sarcoidosis and metastatic lesions: A diagnostic and therapeutic dilemma. Oncology Letters. 2017;**14**(6):7643-7652

[33] Askling J, Grunewald J, Eklund A, Hillerdal G, Ekbom A. Increased risk for cancer following sarcoidosis. American Journal of Respiratory and Critical Care Medicine. 1999;**160**:1668-1672

[34] Boffetta P, Rabkin CS, Gridley G. A cohort study of cancer among

sarcoidosis patients. International Journal of Cancer. 2009;**124**:2697-2700

[35] Cohen PR, Kurzrock R. Sarcoidosis and malignancy. Clinics in Dermatology. 2007;**25**(3):326-333

[36] Sehgal S, Goyal P, Ghosh S, et al. Malignancy and granulomatosis: Causality or coincidence? Narrative systematic review. Iranian Journal of Pathology. 2014;**9**:237-244

[37] Brincker H. The sarcoidosis-lymphoma syndrome. British Journal of Cancer. 1986;**54**(3):467-473

[38] Díaz Del Arco C, Aceñero MJ. Sarcoid reaction: A rare occurrence associated to colon adenocarcinoma (case report and literature review). Journal of Gastrointestinal Oncology. 2016;**7**(4):E72-E76