

Case Report

Concurrent Diagnoses of Cutaneous Sarcoidosis and Recurrent Metastatic Breast Cancer: More than a Coincidental Occurrence?

Jacqueline Deen ¹, Nick Mellick,² and Laura Wheller³

¹Department of Dermatology, Sunshine Coast University Hospital, 6 Doherty Street, Birtinya, Queensland 4575, Australia

²Department of Pathology, Medlab Pathology, 280 Newmarket Road, Wilston, Queensland 4051, Australia

³Department of Dermatology, Mater Misericordiae Hospital, Raymond Terrace, South Brisbane, Queensland 4101, Australia

Correspondence should be addressed to Jacqueline Deen; jacqui.deen@gmail.com

Received 17 July 2018; Revised 20 August 2018; Accepted 27 August 2018; Published 5 September 2018

Academic Editor: Jaime A. Tschen

Copyright © 2018 Jacqueline Deen et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Sarcoidosis is a rare, chronic, multisystem disease of unknown aetiology, characterised by non-caseating epithelioid cell granulomas. Its association with internal malignancy, in particular haematological cancers has been strongly documented in the literature, while its link with solid organ malignancies is less extensively reported. We present an atypical case of cutaneous sarcoidosis occurring in association with breast cancer recurrence in a 49-year-old female. Physician recognition of this link between sarcoidosis and internal malignancy is vital because many cases of sarcoidosis in association with neoplasia present initially, or even exclusively, with cutaneous sarcoidal lesions that may precede the development of cancer by several years, or as in our case, present as a cutaneous marker of concomitant underlying malignancy. Our case highlights the importance of age-appropriate cancer screening in addition to a routine work-up for systemic sarcoidosis in a patient with cutaneous sarcoidosis.

1. Introduction

Sarcoidosis is a chronic, idiopathic, multisystem disease, characterised by non-caseating epithelioid cell granulomas. The lungs are involved in more than 90% of cases, but the lymphatic system, eyes, and skin may also be affected. Less common but usually more severe forms can involve the liver, spleen, central nervous system, heart, upper respiratory tract, and bones. Its pathogenesis appears to correspond to an aberrant immune response in a susceptible host. Sarcoidosis typically affects young adults, with a slight female general predominance [1, 2].

Various diseases have been associated with sarcoidosis, including autoimmune disorders such as rheumatoid arthritis, psoriasis, vasculitis, thyroid disease, systemic sclerosis, and Sjogren syndrome. Haematological malignancies, in particular lymphoproliferative disorders such as Hodgkin lymphoma, are most strongly associated with sarcoidosis compared to solid organ malignancies [2, 3]. We present a rare case of cutaneous sarcoidosis occurring in association with breast carcinoma.

2. Case Report

A 49-year-old female presented with a 2-month history of asymptomatic lesions on the left knee found incidentally on routine full skin examination. The patient was otherwise well, with no pulmonary or systemic symptoms.

She had a past history of breast cancer diagnosed 4 years ago, managed by lumpectomy and adjuvant chemoradiotherapy achieving remission. The patient had regular cancer surveillance and was currently on adjuvant tamoxifen, with a planned duration of 10 years. Her other notable medical history included lifelong asthma, gastrooesophageal reflux disease, depression, subacute thyroiditis and previous shoulder, and knee arthroscopies. Her regular medications included tamoxifen, pantoprazole, venlafaxine, budesonide/formoterol, and terbutaline. She was a lifetime non-smoker and rarely consumed alcohol. The patient had no family history of autoimmune conditions.

Examination revealed numerous erythematous-to-brown, non-tender papules occurring on the anterior left knee (Figure 1). On the right foot, at the site of a scar

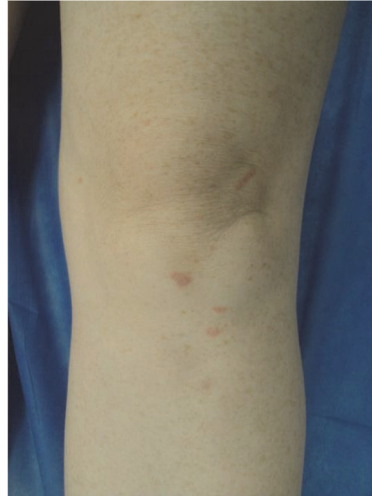


FIGURE 1: Clinical photograph showing numerous erythematous-to-brown papules on the anterior left knee.

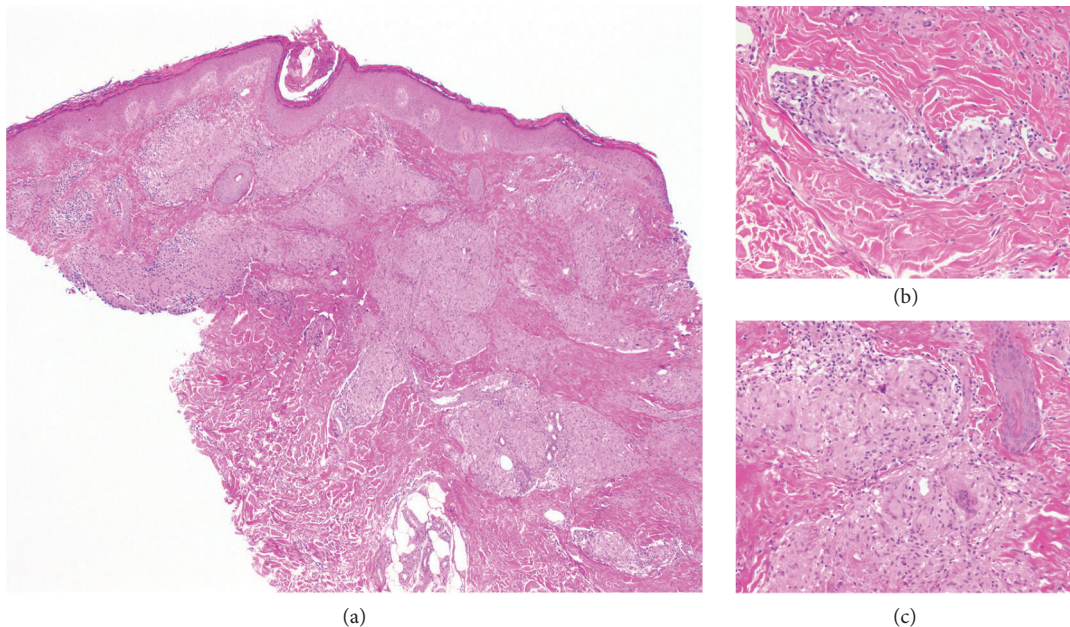


FIGURE 2: (a, b and c) Histology of left knee lesion showing a sarcoidal-type granulomatous reaction. (a) Much of the reticular dermis is occupied by a granulomatous infiltrate (hematoxylin and eosin staining, original magnification x40). (b and c) Individual granulomas are sarcoidal in type, i.e., non-necrotizing with a minimal associated lymphocytic infiltrate (so-called “naked” granulomas) (hematoxylin and eosin staining, original magnification x200).

from prior cryotherapy for plantar warts, the patient had a similar area of firm indurated erythematous-to-brown change. Dermoscopy of both sites showed orange and yellow translucent globules (“apple-jelly” sign). There were no skin lesions detected on full skin examination suspicious for malignancy. There was no lymphadenopathy and systemic examination was otherwise unremarkable.

Skin biopsy showed multiple, variably sized naked sarcoidosis type granulomas scattered throughout the dermis (Figure 2). Chest radiograph showed bilateral hilar lymphadenopathy and serum angiotensin-converting enzyme was elevated at 107 U/L. Other laboratory tests were within

normal limits (full blood count, liver and renal function tests, and calcium and inflammatory markers). Further investigations excluded systemic sarcoidosis (cardiac MRI and CT-PET scan). The CT PET ordered during systemic work-up, however, showed a solitary lesion in the T10 vertebra and subsequent biopsy proved recurrent metastatic breast cancer.

The patient’s management was then deferred to a medical oncologist for ongoing care of her metastatic breast cancer. She received stereotactic radiation to her spinal lesion and was commenced on a special access program with ribociclib. Following breast cancer treatment, cutaneous sarcoidal lesions completely resolved.

TABLE 1: Previous literature cases of breast cancer and sarcoidosis.

| Reference | Sex | Patient age (years) | Interval b/t diseases (years) | Sarcoidosis onset* | Tumour type |
|--------------------------------------|-----|---------------------|-------------------------------|--------------------|---|
| Prior et al. (1952) [6] | F | 59 | 5 | P | Breast adenocarcinoma |
| Brincker et al. (1974) [5] | F | NS | NS | P | NS |
| | F | | | P | |
| | F | | | P | |
| | M | | | P | |
| Suen JS et al (1990) [7] | F | 50 | 0.7 | A | Breast cancer (stage II) |
| Shah AK et al (1990) [8] | F | 36 | 3 | P | Invasive ductal carcinoma |
| Von Knorring et al. (1976) [9] | F | 74 | 5 | P | Non-metastasizing breast carcinoma |
| Whittington R et al. (1986) [10] | F | 52 | 0.6 | A | Infiltrating ductal carcinoma |
| | F | 42 | 5 | P | Metastatic breast cancer |
| Reich J et al. (1995) [11] | F | 47 | 10 | A | Intraductal breast carcinoma |
| | F | 55 | 9 | P | Infiltrating ductal breast carcinoma |
| Brechtel B et al. (1996) [4] | F | 58 | 1 | P | NS |
| Seersholm N et al. (1997) [12] | NS | NS | NS | P | NS |
| Romer FK et al. (1998) [13] | F | Between 19-78 years | NS | P | NS |
| | F | | | P | |
| | F | | | P | |
| | F | | | P | |
| | F | | | P | |
| | F | | | P | |
| Askling J et al. (1999) [14] | NS | NS | NS | P | NS |
| | NS | | | P | NS |
| Lower EE et al. (2001) [15] | F | 25 | 5 | P | Invasive ductal carcinoma |
| | F | 57 | 5 | P | Infiltrating ductal carcinoma |
| | F | 58 | 8 | P | Invasive ductal carcinoma |
| | F | 40 | 2 | A | Invasive ductal carcinoma |
| | F | 49 | 1 | A | Invasive ductal carcinoma |
| | F | 38 | 2 | A | Invasive ductal carcinoma |
| | F | 36 | 1 | A | Invasive ductal carcinoma |
| | F | 57 | 8 | A | Invasive ductal carcinoma |
| | F | 55 | 0 | C | Invasive ductal carcinoma |
| | F | 43 | 0 | C | Intraductal carcinoma |
| Garcia et al. (2003) [16] | F | 44 | 3 | P | Invasive lobular breast carcinoma with ductal and mucinous features |
| Chen W et al. (2004) [17] | F | NS | NS | P | NS |
| | F | NS | 0 | C | NS |
| Van der Hoeven JJ et al. (2004) [18] | F | NS | 0 | C | Ductal carcinoma of breast |
| Gusakova I et al. (2007) [19] | F | 69 | 6 | A | Infiltrating ductal carcinoma of breast |
| | F | 60 | 4 | A | Infiltrating ductal carcinoma of breast |

TABLE 1: Continued.

| Reference | Sex | Patient age (years) | Interval b/t diseases (years) | Sarcoidosis onset* | Tumour type |
|-----------------------------------|-----|---------------------|-------------------------------|--------------------|---|
| Tolaney SM et al. (2007) [20] | F | 47 | 0 | C | Invasive lobular carcinoma of breast |
| | F | 51 | 2 | A | Invasive ductal carcinoma |
| | F | 31 | 0 | C | Invasive ductal carcinoma |
| Ataergin S et al. (2009) [21] | F | 75 | 12 | A | Breast cancer (T3N1M0) |
| Viswanath L et al. (2009) [22] | F | 50 | 2 | A | Infiltrating ductal carcinoma breast |
| Ito T et al. (2010) [23] | F | 90 | 6 | A | Metastatic breast cancer |
| | F | 52 | 4 | A | Invasive ductal carcinoma breast |
| Alexandrescu DT et al. (2011) [1] | F | 72 | 8 | P | NS |
| | F | 46 | 4 | P | NS |
| | F | 46 | 5 | P | Infiltrating ductal carcinoma of breast |
| Bush E et al. (2011) [24] | F | 42 | 0 | C | Infiltrating ductal carcinoma of breast |
| Nishioka M et al (2012) [25] | F | 79 | 0 | C | Recurrent breast cancer (local) |
| DeFilippis EM et al (2013) [26] | F | 63 | 0 | C | Stage 1 breast cancer |
| Akhtari et al. (2014) [27] | F | 47 | 0 | C | Ductal invasive carcinoma |
| Kim et al. (2014) [28] | F | 44 | 2 | A | Ductal invasive carcinoma |
| Zivin et al. (2014) [29] | F | 32 | 0 | C | Ductal invasive carcinoma |
| Altinkaya et al. (2015) [30] | F | 70 | 0 | C | Ductal invasive carcinoma |
| Conte et al. (2015) [31] | F | 50 | 0 | C | Ductal invasive carcinoma |
| El Hammoumi (2015) [32] | F | 51 | 3 | A | Lobular carcinoma breast |
| Chen J et al. (2015) [33] | F | 62 | 7 | A | Infiltrating ductal carcinoma |
| | F | 54 | 0 | C | Infiltrating ductal carcinoma |
| | F | 50 | 24 | P | Infiltrating ductal carcinoma |
| | F | 63 | 34 | P | Infiltrating ductal carcinoma |
| | F | 77 | 9 | P | Infiltrating ductal carcinoma |
| Present case | F | 49 | 0 | C | Recurrent metastatic breast cancer |

F: female, patient age: age at concurrent disease diagnosis, interval b/t diseases: interval between both diseases (sarcoidosis and breast cancer).

*P: **preceded** breast cancer diagnosis; C: occurred **concomitantly** with breast cancer diagnosis; A: occurred **after** breast cancer diagnosis.

3. Discussion

Cutaneous involvement presents in 25% of patients with systemic sarcoidosis and may be the only manifestation [4]. Dermatologists are frequently the first clinicians to identify sarcoidosis as specific skin lesions are often the presenting sign and skin biopsy enables early diagnosis. Skin lesions are extremely variable and may be specific or nonspecific. Specific lesions are those that histologically display noncaseating granulomas, which manifest clinically as maculopapules, plaques, lupus pernio, scar-sarcoidosis, and subcutaneous sarcoidosis. Nonspecific lesions lack histological evidence of sarcoid granulomas and the most significant lesions are erythema nodosum. In isolated cutaneous disease, further evaluation is essential as transformation into systemic sarcoidosis occurs in approximately one-third of patients within three years [1, 2].

Various diseases have been associated with sarcoidosis. Previously, an association between sarcoidosis and malignancy has been described, although no clear relationship has been identified. In most cases, sarcoidosis was diagnosed before the detection of an associated neoplasm. Haematological malignancies remain most strongly associated compared to solid tumours [1–3]. Brincker and Wilbek in 1974 were first to describe this association, reporting that, in patients with sarcoidosis, lymphoma occurred 11 times more frequently and lung cancer occurred three times more frequently compared with the general population [5].

Previous literature cases of sarcoidosis occurring with breast cancer are summarised in Table 1. The average patient age was 53 years, with 98.3% being female. In 30 (48.4%) patients the identification of sarcoidosis preceded the diagnosis of breast cancer; in 18 (29.0%) patients breast cancer diagnosis preceded sarcoidosis; and in 14 (22.6%) patients

both diseases occurred concomitantly. The average time interval between the diagnosis of sarcoidosis and breast cancer was 8.3 years (range 1-34 years). When breast cancer predated sarcoidosis, the average interval was 4.1 years (range 0.6-12 years). In our case, the patient age at diagnosis was 49 years, which is similar to what was described in the literature.

Our case is unique in that the cutaneous sarcoidosis most likely occurred around the same time the patient's breast cancer recurrence was diagnosed and investigation for systemic sarcoidosis revealed her metastatic disease. This may be an incidental finding or indicate that dysregulation of the immune system mediated by either the breast cancer or sarcoidosis lead to the granulomatous inflammation of sarcoidosis or neoplasm, respectively [3, 4, 34]. In addition, there was complete resolution of the cutaneous sarcoid lesions following treatment of the patient's metastatic breast cancer, strengthening the correlation between both entities.

Recognition by physicians of this link between sarcoidosis and internal malignancy is vital because many cases of sarcoidosis in association with neoplasia present initially, or even exclusively, with cutaneous sarcoid lesions that may precede the development of cancer by several years or as in our case, present as a cutaneous marker of concomitant underlying malignancy. Thus, in addition to routine screening for systemic sarcoidosis, patients diagnosed with cutaneous sarcoidosis should be closely followed up, particularly including age-appropriate cancer screening to exclude the development of associated malignancy [1].

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

- [1] D. T. Alexandrescu, C. Lisa Kauffman, T. E. Ichim, N. H. Rior-dan, F. Kabigting, and C. A. Dasanu, "Cutaneous sarcoidosis and malignancy: An association between sarcoidosis with skin manifestations and systemic neoplasia," *Dermatology Online Journal*, vol. 17, no. 1, 2011.
- [2] A. Grados, M. Ebbo, E. Bernit et al., "Sarcoidosis occurring after solid cancer: a nonfortuitous association: report of 12 cases and review of the literature," *Medicine (United States)*, vol. 94, no. 28, article no. e928, 2015.
- [3] M. D. Schweitzer, O. Salamo, G. Holt, E. Donna, and M. Mirsaeidi, "Sarcoidosis onset after breast cancer; a potential association," *European Journal of Internal Medicine*, vol. 44, pp. e11-e12, 2017.
- [4] B. Brechtel, N. Haas, B. M. Henz, and G. Kolde, "Allopurinol: A therapeutic alternative for disseminated cutaneous sarcoidosis," *British Journal of Dermatology*, vol. 135, no. 2, pp. 307-309, 1996.
- [5] H. Brincker and E. Wilbek, "The incidence of malignant tumours in patients with respiratory sarcoidosis," *British Journal of Cancer*, vol. 29, no. 3, pp. 247-251, 1974.
- [6] J. T. Prior, "Boeck's sarcoid with coexisting carcinoma," *The American Journal of Surgery*, vol. 83, no. 2, pp. 201-204, 1952.
- [7] J. S. Suen, M. S. Forse, R. H. Hyland, and C. K. Chan, "The malignancy-sarcoidosis syndrome," *CHEST*, vol. 98, no. 5, pp. 1300-1302, 1990.
- [8] A. K. Shah, L. Solomon, and M. A. Gumbs, "Sarcoidosis of the breast coexisting with mammary carcinoma," *New York State Journal of Medicine*, vol. 90, no. 6, pp. 331-333, 1990.
- [9] J. von Knorring and O. Selroos, "Sarcoidosis with thyroid involvement, polymyalgia rheumatica and breast carcinoma: A case report," *Scandinavian Journal of Rheumatology*, vol. 5, no. 2, pp. 77-80, 1976.
- [10] R. Whittington, A. Lazarus, S. Nerenstone, and A. Martin, "Sarcoidosis developing during therapy for breast cancer," *CHEST*, vol. 89, no. 5, pp. 762-763, 1986.
- [11] J. M. Reich, J. P. Mullooly, and R. E. Johnson, "Linkage analysis of malignancy-associated sarcoidosis," *CHEST*, vol. 107, no. 3, pp. 605-613, 1995.
- [12] N. Seersholm, J. Vestbo, and K. Viskum, "Risk of malignant neoplasms in patients with pulmonary sarcoidosis," *Thorax*, vol. 52, no. 10, pp. 892-894, 1997.
- [13] F. K. Rømer, P. Hommelgaard, and G. Schou, "Sarcoidosis and cancer revisited: a long-term follow-up study of 555 Danish sarcoidosis patients," *European Respiratory Journal*, vol. 12, no. 4, pp. 906-912, 1998.
- [14] J. Askling, J. Grunewald, A. Eklund, G. Hillerdal, and A. Ekblom, "Increased risk for cancer following sarcoidosis," *American Journal of Respiratory and Critical Care Medicine*, vol. 160, no. 5, part 1, pp. 1668-1672, 1999.
- [15] E. E. Lower, H. H. Hawkins, and R. P. Baughman, "Breast disease in sarcoidosis," *Sarcoidosis Vasculitis and Diffuse Lung Diseases*, vol. 18, no. 3, pp. 301-306, 2001.
- [16] C. A. Garcia, R. J. Rosenberg, and R. P. Spencer, "FDG-Positron Emission Tomographic Imaging in Carcinoma of the Breast: Interference by Massive Sarcoidosis," *Clinical Nuclear Medicine*, vol. 28, no. 3, pp. 218-219, 2003.
- [17] W. Chen, R. A. Miller, and K. A. Hebbe, "Sarcoidosis and breast carcinoma: three case reports and review," *Journal of Clinical Oncology*, pp. 22-867, 2004.
- [18] J. J. M. Van Der Hoeven, N. C. Krak, O. S. Hoekstra et al., "18F-2-fluoro-2-deoxy-D-glucose positron emission tomography in staging of locally advanced breast cancer," *Journal of Clinical Oncology*, vol. 22, no. 7, pp. 1253-1259, 2004.
- [19] I. Gusakova, K. Lavrenkov, S. Ariad, and W. Mermershtain, "Pulmonary sarcoidosis mimicking metastases in breast cancer patients," *Onkologie*, vol. 30, no. 6, pp. 327-328, 2007.
- [20] S. M. Tolaney, Y. L. Colson, R. R. Gill et al., "Sarcoidosis mimicking metastatic breast cancer," *Clinical Breast Cancer*, vol. 7, no. 10, pp. 804-810, 2007.
- [21] S. Ataergin, N. Arslan, A. Ozet, and M. A. Ozguven, "Abnormal 18F-FDG Uptake Detected with Positron Emission Tomography in a Patient with Breast Cancer: A Case of Sarcoidosis and Review of the Literature," *Case Reports in Medicine*, vol. 2009, Article ID 785047, 4 pages, 2009.
- [22] L. Viswanath, S. Pallade, B. Krishnamurthy et al., "Darier-Roussy Sarcoidosis Mimicking Metastatic Breast Cancer," *Case Reports in Oncology*, vol. 2, no. 3, pp. 251-254, 2009.
- [23] T. Ito, T. Okada, K. Murayama et al., "Two cases of sarcoidosis discovered accidentally by positron emission tomography in patients with breast cancer," *The Breast Journal*, vol. 16, no. 5, pp. 561-563, 2010.
- [24] E. Bush, D. Lamonica, and T. O'Connor, "Sarcoidosis mimicking metastatic breast cancer," *The Breast Journal*, vol. 17, no. 5, pp. 533-535, 2011.
- [25] M. Nishioka, K. Igawa, Y. Yahata, M. Tani, and I. Katayama, "Simultaneous occurrence of dermatomyositis and systemic

- sarcoidosis with recurrent breast cancer,” *The Journal of Dermatology*, vol. 39, no. 5, pp. 485-486, 2012.
- [26] E. M. DeFilippis and E. K. Arleo, “New diagnosis of sarcoidosis during treatment for breast cancer, with radiologic-pathologic correlation,” *Clinical Imaging*, vol. 37, no. 4, pp. 762–766, 2013.
- [27] M. Akhtari, J. R. Quesada, M. R. Schwartz, S. B. Chiang, and B. S. Teh, “Sarcoidosis presenting as metastatic lymphadenopathy in breast cancer,” *Clinical Breast Cancer*, vol. 14, no. 5, pp. e107–e110, 2014.
- [28] H. S. Kim, S.-Y. Lee, S. C. Oh, C. W. Choi, J. S. Kim, and J. H. Seo, “Case report of pulmonary sarcoidosis suspected to be pulmonary metastasis in a patient with breast cancer,” *Cancer Research and Treatment*, vol. 46, no. 3, pp. 317–321, 2014.
- [29] S. Zivin, O. David, and Y. Lu, “Sarcoidosis mimicking metastatic breast cancer on FDG PET/CT,” *Internal Medicine*, vol. 53, no. 21, pp. 2555-2556, 2014.
- [30] M. Altinkaya, N. Altinkaya, and B. Hazer, “Sarcoidosis mimicking metastatic breast cancer in a patient with early-stage breast cancer,” *Turkish Journal of Surgery*, vol. 32, no. 1, pp. 71–74, 2016.
- [31] G. Conte, F. Zugni, M. Colleoni, G. Renne, M. Bellomi, and G. Petralia, “Sarcoidosis with bone involvement mimicking metastatic disease at ¹⁸F-FDG PET/CT: Problem solving by diffusion whole-body MRI,” *ecancermedicalscience*, vol. 9, 2015.
- [32] M. El Hammoumi, M. El Marjany, D. Moussaoui, A. Doudouh, H. Mansouri, and E. H. Kabiri, “Mediastinal sarcoidosis mimicking lymph malignancy recurrence after anti-neoplastic therapy,” *Archivos de Bronconeumología*, vol. 51, no. 7, pp. e33–e35, 2015.
- [33] J. Chen, R. Carter III, D. Maoz, A. Tobar, E. Sharon, and F. Greif, “Breast cancer and sarcoidosis: Case series and review of the literature,” *Breast Care*, vol. 10, no. 2, pp. 137–140, 2015.
- [34] P. R. Cohen and R. Kurzrock, “Sarcoidosis and malignancy,” *Clinics in Dermatology*, vol. 25, no. 3, pp. 326–333, 2007.