Systemic sarcoidosis during pazopanib treatment for clear cell renal cell carcinoma

Dear Editor,

Sarcoidosis is a multi-organ disease of unknown aetiology, that preferentially affects middle-aged females. It can manifest in almost any organ, such as the lungs, heart, skin and eyes. Cutaneous lesions occur in about 30% of sarcoid patients, presenting as papules, nodules, plaques, ulcers and alopecia.[1] The association with malignancies has already been reported. The diagnosis of sarcoidosis may precede or occur after malignancy. It can have a paraneoplastic origin or it can be triggered by antineoplastic treatments.[2] Here we present a case of a 64-year-old woman who was referred to our department for the appearance of skin lesions. Approximately 12 years ago, she was diagnosed with clear cell renal cell carcinoma, Fuhrman grade II. Eight years later, vertebral metastases were found. Given the poor response to radiotherapy, tyrosine kinase inhibitor, pazopanib was started. After two years of treatment, a computer tomography scan revealed two millimetric nodules in the inferior lobe of the right lung, without lymphadenopathy. These lesions showed a slight increase in size at one-year follow-up, together with the appearance of similar new lesions in the middle and upper right lobes and multiple mediastinal lymphadenomegaly. "Tree in bud" parenchymal thickening was also detected [Figure 1]. Over a period of six months, imaging techniques highlighted a progressive involvement of the lungs and the onset of micronodular splenomegaly. Positron emission tomography showed hypermetabolic activity in the lungs, spleen and several lymph nodes (including supraclavicular, mediastinal and inguinal ones). Mediastinal lesions were partially responsive to systemic steroids; hence a supraclavicular lymph node biopsy was performed. Histology showed epithelioid granulomatous lymphadenopathy, without necrosis. After three months, several asymptomatic coalescing papules appeared on the forehead, on the root of the nose and on the posterior neck region. They were yellowish in colour with irregular surfaces, ill-defined borders and an overall diameter between 15 and 25 mm. Some thin vessels were visible to the naked eye [Figures 2a and b]. Dermoscopy revealed structureless yellow-orange areas, well-focused linear irregular vessels and dilated follicles [Figure 2c]. Histology confirmed the diagnostic suspicion of sarcoidosis [Figures 3a and b]. Because of the rapid worsening of the general condition, the patient was lost at follow-up. We eventually found out about the patient's demise.

The association between cancer and sarcoidosis is well known. Linkage analysis revealed that sarcoidosis and malignancies may be aetiologically related in at least 25% cases.[3] Sarcoidosis-related tumours include haematologic malignancies and solid cancers (e.g., liver, lung, skin, testicle, cervix and uterus). Reports about sarcoidosis and renal cell carcinoma are very limited. Granulomatous reactions associated with clear cell renal cell carcinoma in literature are mainly represented by sarcoid-like granulomas, non-necrotizing collections of epithelioid cells found in oncologic patients not fulfilling diagnostic criteria for

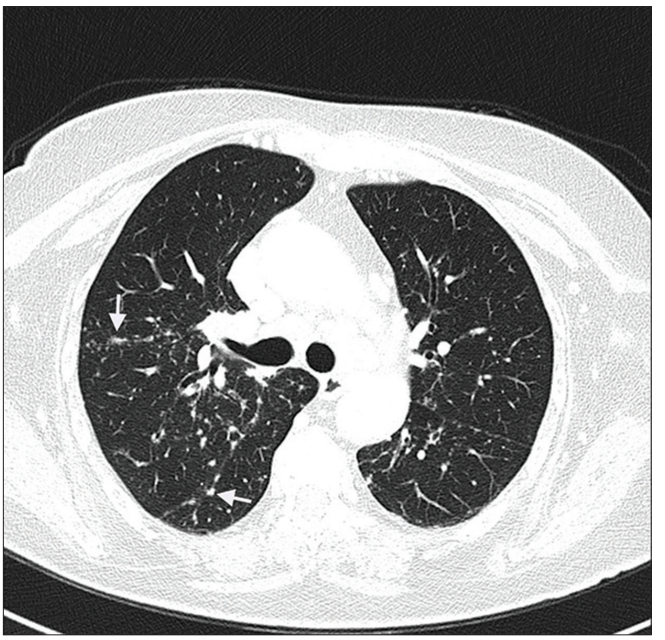

Figure 1: Multiple small sub-pleural, peri-bronchovascular and centrilobular nodules (arrows) in the lungs with multiple mediastinal lymphadenopathies (CT scan)

How to cite this article: Vaccaro M, Borgia F, Lentini M, Gaeta M, Marafioti I. Systemic sarcoidosis during pazopanib treatment for clear cell renal cell carcinoma. Indian J Dermatol Venereol Leprol 2023;89:444-6.

Received: June, 2021 **Accepted:** July, 2022 **EPub Ahead of Print:** December, 2022 **Published:** April, 2023

DOI: 10.25259/IJDVL_599_2021 **PMID:** 36688889

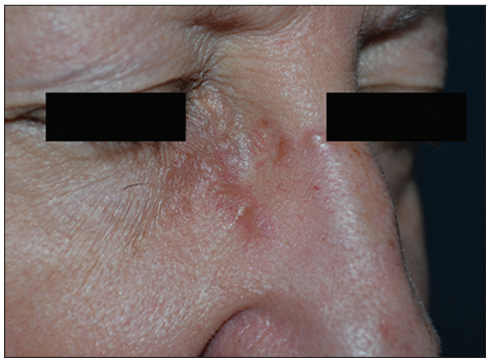

Figure 2a: Structureless orange areas with well-focused linear irregular vessels and dilated follicles on dermoscopy (×20)

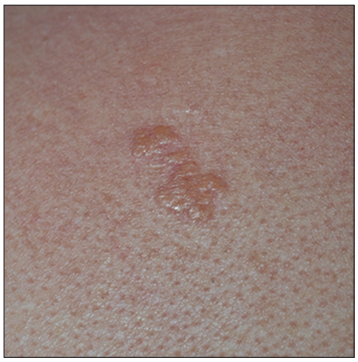

Figure 2b: Sarcoidosis skin lesions on the back of the neck

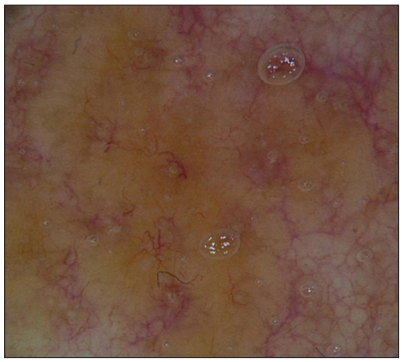

Figure 2c: Dermoscopy showed structureless yellowish-orange areas and well-focused linear irregular vessels (×20)

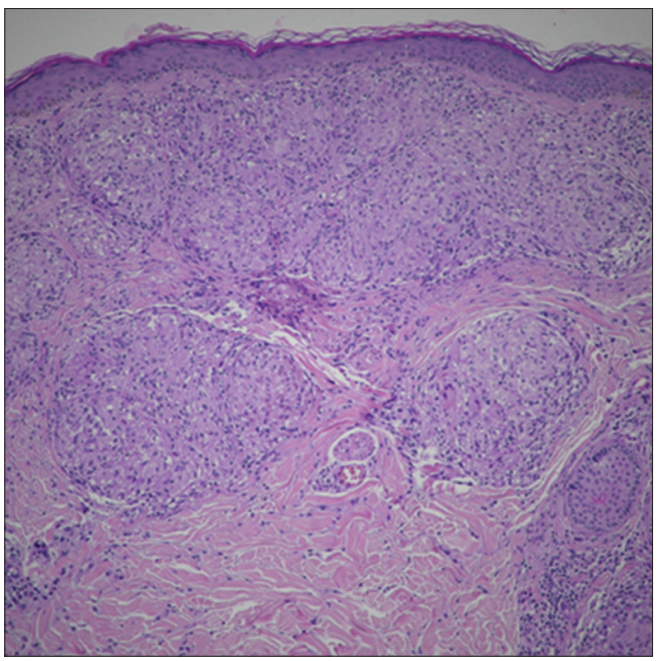

Figure 3a: Sharply defined "naked" sarcoidal granulomas with sparse few lymphocytes and no necrosis (H&E, ×200)

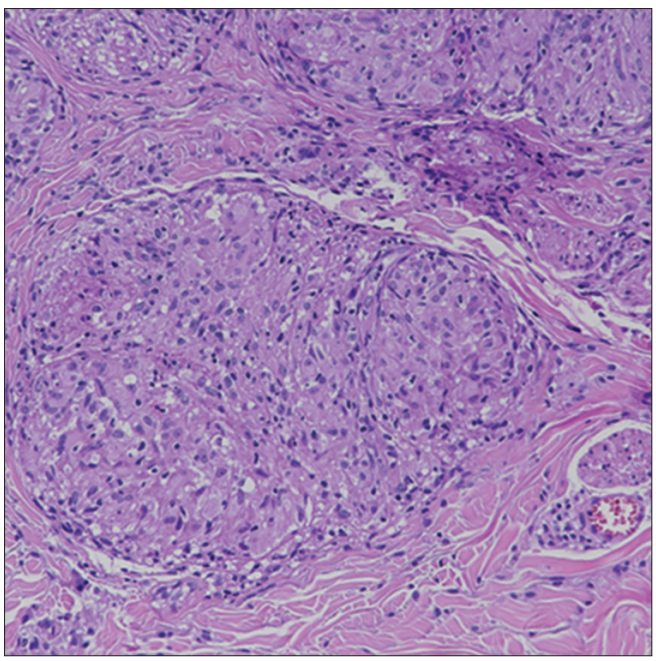

Figure 3b: "Naked" granuloma is sharply defined with sparse lymphocytes and no necrosis, consistent with sarcoidal granuloma (H&E, ×400)

systemic sarcoidosis.[4] They occur in 4.4% of carcinomas, 13.8% of Hodgkin and 7.3% of non-Hodgkin lymphomas.[5] Sarcoid-like granulomata (SLGs) can arise in regional draining lymph nodes, spleen, bone marrow and skin but also in both primary or metastatic neoplastic tissue. They have been interpreted as a T-cell response to antigenic factors released by tumour cells during necrosis.[6] The distinction between sarcoidosis and sarcoid-like granuloma is important in establishing the risk of systemic disease. They both show fluorodeoxyglucose avidity mimicking malignancy dissemination, so histologic confirmation is always needed. Sarcoid-like granulomas differ from sarcoidosis granulomas by the presence of B-cells, prominent sinus histiocytosis and poor fibrosis. In our patient, the onset of lung disease appeared after two years' of treatment with pazopanib. It is known that some antineoplastic drugs, including pembrolizumab, ipilimumab, nivolumab, interferon and interleukin-2, can induce or exacerbate sarcoidosis, especially in patients with haematologic malignancies. But until now, pazopanib has not been reported as a causative drug.[2] Moreover, its mechanism of action does not explain the onset of the disease. Discontinuation of chemotherapy should be useful to distinguish a drug-related reaction from a disease-related one, avoiding biopsy. Unfortunately, this is often not possible since life-saving drugs are involved. Our case showed a very rare association between clear cell renal cell carcinoma and systemic sarcoidosis in the course of treatment with pazopanib. Although it is not possible to establish with certainty whether sarcoidosis was primary or secondary to the tumour or its treatment, our experience seemed worthy of note. Supported by the literature data in oncologic patients, an aetiological correlation between sarcoidosis and the underlying renal carcinoma seems the most likely hypothesis, while treatment with pazopanib is probably temporal rather than causally related to the systemic disease. However, the rapid progression of granulomatous

manifestations after pazopanib therapy, does not allow to exclude its negative influence on the course of sarcoidosis.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship
Nil.

Conflict of interest
There are no conflicts of interest.

Mario Vaccaro, Francesco Borgia, Maria Lentini[1], Michele Gaeta[2], Ilenia Marafioti

Departments of Clinical and Experimental Medicine, Dermatology, [1]Human Pathology, [2]Biomedical, Dental Science and Morphological and Functional Images, Radiology Unit, University of Messina, Messina, Italy.

Corresponding author:
Dr. Ilenia Marafioti,
Via C. Valeria, Gazzi. 98125 Messina,
Italy.
ileniamarafioti@gmail.com

References

1. Noe MH, Rosenbach M. Cutaneous sarcoidosis. Curr Opin Pulm Med 2017;23:482–6.
2. Cohen PR, Kurzrock R. Sarcoidosis and malignancy. Clin Dermatol 2007;25:326–33.
3. Reich JM, Mullooly JP, Johnson RE. Linkage analysis of malignancy-associated sarcoidosis. Chest 1995;107:605–13.
4. The Japanese Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG) Diagnostic Standard and Guideline for Sarcoidosis-2015, <http://jssog.com/www/top/shindan/shindan2-1new.html>.
5. Brincker H. Sarcoid reactions in malignant tumours. Cancer Treat Rev 1986;13:147–56.
6. Kamiyoshihara M, Hirai T, Kawashima O, Ishikawa S, Morishita Y. Sarcoid reactions in primary pulmonary carcinoma: Report of seven cases. Oncol Rep 1998;5:177–80.

Unilateral nodular malignant melanoma with in-transit metastasis over lower limb masquerading as vascular tumours: A unique presentation

Dear Editor,

A 50-year-old man presented to outpatient department of dermatology, All India Institute of Medical Sciences, Bhubaneswar, with multiple asymptomatic, pigmented, nodular lesions over right lower limb. Initially, there was a single nodular lesion near the right ankle one year ago, which had been excised at a local hospital. He gradually developed multiple new nodules over the same limb in a linear fashion starting from lower part in a span of seven–eight months. The whole limb was swollen and enlarged. He had undergone surgery in the right inguinal region eight months ago. There was no history of any constitutional symptoms, weight loss, loss of appetite or respiratory symptoms. On dermatological examination, multiple dome-shaped, smooth, glossy, pigmented, firm, non-tender, 2–3 mm nodular lesions and 4 cm × 7 cm plaques were found on the right lower limb with underlying skin showing woody-hard induration. The lesions were showing verrucosity, ulceration and crusting on surface [Figures 1a and b].

There was bilateral enlarged inguinal lymphadenopathy with firm-to-hard, discrete nodes of 2–3 cm size. General and systemic examination revealed no abnormality. Routine hematologic and biochemical investigations were within normal limits except for the presence of anaemia (Hb - 7.4 g/dl). His serology for HIV, HBsAg and HCV was normal. Kaposi sarcoma, angiosarcoma and nodular melanoma were considered as differential diagnoses. Other investigations such as chest X-ray, ultrasonography of abdomen and pelvis, computed tomography scan of abdomen and pelvis and magnetic resonance imaging of spine for metastasis were found to be normal. MRI of right leg showed lobulated swellings in cutaneous and subcutaneous planes. On histopathological examination, sections showed a proliferative growth in the upper dermis with plenty of tumour cells, that were polygonal with hyperchromatic nuclei, perinuclear halo, prominent nucleoli and increased mitotic activity [Figures 2a and 2b]. Melanin

How to cite this article: Sahu K, Sirka CS, Sethy M, Mishra JJ. Unilateral nodular malignant melanoma with in-transit metastasis over lower limb masquerading as vascular tumours: A unique presentation. Indian J Dermatol Venereol Leprol 2023;89:446-9.

Received: December, 2020 **Accepted:** November, 2021 **EPub Ahead of Print:** December, 2022 **Published:** April, 2023

DOI: 10.25259/IJDVL_568_20 **PMID:** 36688882