Occurrence of Acute Myeloid Leukaemia in a Patient with Cutaneous Sarcoidosis

Manikoth Payyanadan Binitha, Anza Khader, Mohamed Shaan, Ahmed Nadeem

Department of Dermatology and Venereology, Government Medical College, Kozhikode, Kerala*

ABSTRACT

Published on 27th September 2017

There is a close relationship between sarcoidosis and malignancy, which is more pronounced in patients with cutaneous sarcoidosis. An intense T helper cell response occurs in sarcoidosis, with an imbalance between the activity of effector and regulatory T cells, which could be responsible for the coexistence of malignancy. We present a patient who developed acute myeloid leukaemia one and a half years after she was diagnosed with cutaneous sarcoidosis.

Keywords: Cutaneous Sarcoidosis, Acute Myeloid Leukaemia

*See End Note for complete author details

INTRODUCTION

Sarcoidosis is a granulomatous disorder which can present in myriad forms. A strong link between sarcoidosis and malignancy has been noticed, in the form of one being followed or preceded by the other. It has been suggested that the risk of developing malignancy is higher in patients with cutaneous sarcoidosis than in those without skin lesions.[1] We present a patient who was diagnosed as a case of purely cutaneous sarcoidosis, who presented with acute myeloid leukaemia, one and a half years after the initial diagnosis.

CASE REPORT

A 23-year-old otherwise healthy woman presented in December 2013, with an asymptomatic lesion on the face of nine months duration. There was no history of any other skin lesions or systemic symptoms.

General examination was unremarkable. Dermatological examination revealed a large, well-defined violaceous plaque on the left cheek extending upwards to the forehead and downwards to the sub-mental region and right cheek **(figure 1)**. The surface showed telangiectasia and mild scaling. The periphery of the lesion showed multiple erythematous papules, indicating extension of the lesion. The lesions demonstrated a yellow colour on diascopy. There was no mucosal involvement, parotid swelling, sensory loss or peripheral nerve thickening. Systemic examination was normal.

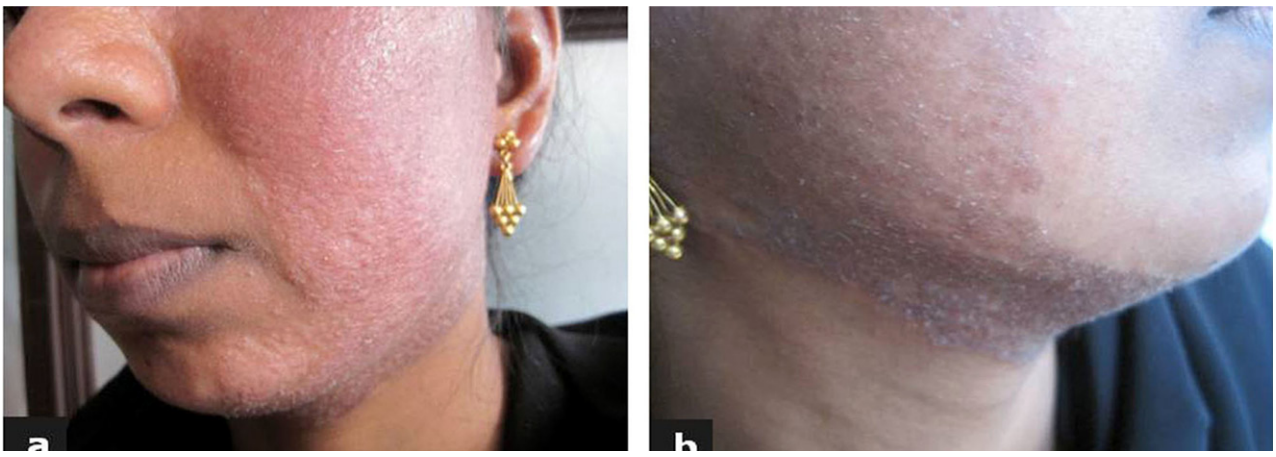

Figure 1. **A large violaceous, mildly scaly plaque on the left cheek, extending to the right side of the face**

Cite this article as: Binitha MP, Khader A, Shaan M, Nadeem A. Occurrence of Acute Myeloid Leukaemia in a Patient with Cutaneous Sarcoidosis. Kerala Medical Journal. 2017 Sep 27;10(3):125–9.

Corresponding Author:
Dr M P Binitha, Haritha, Post Beypore, Kozhikode, Kerala, India – 673015. Phone: 04952414444, 9447539177
Email: mpbinitha56@gmail.com

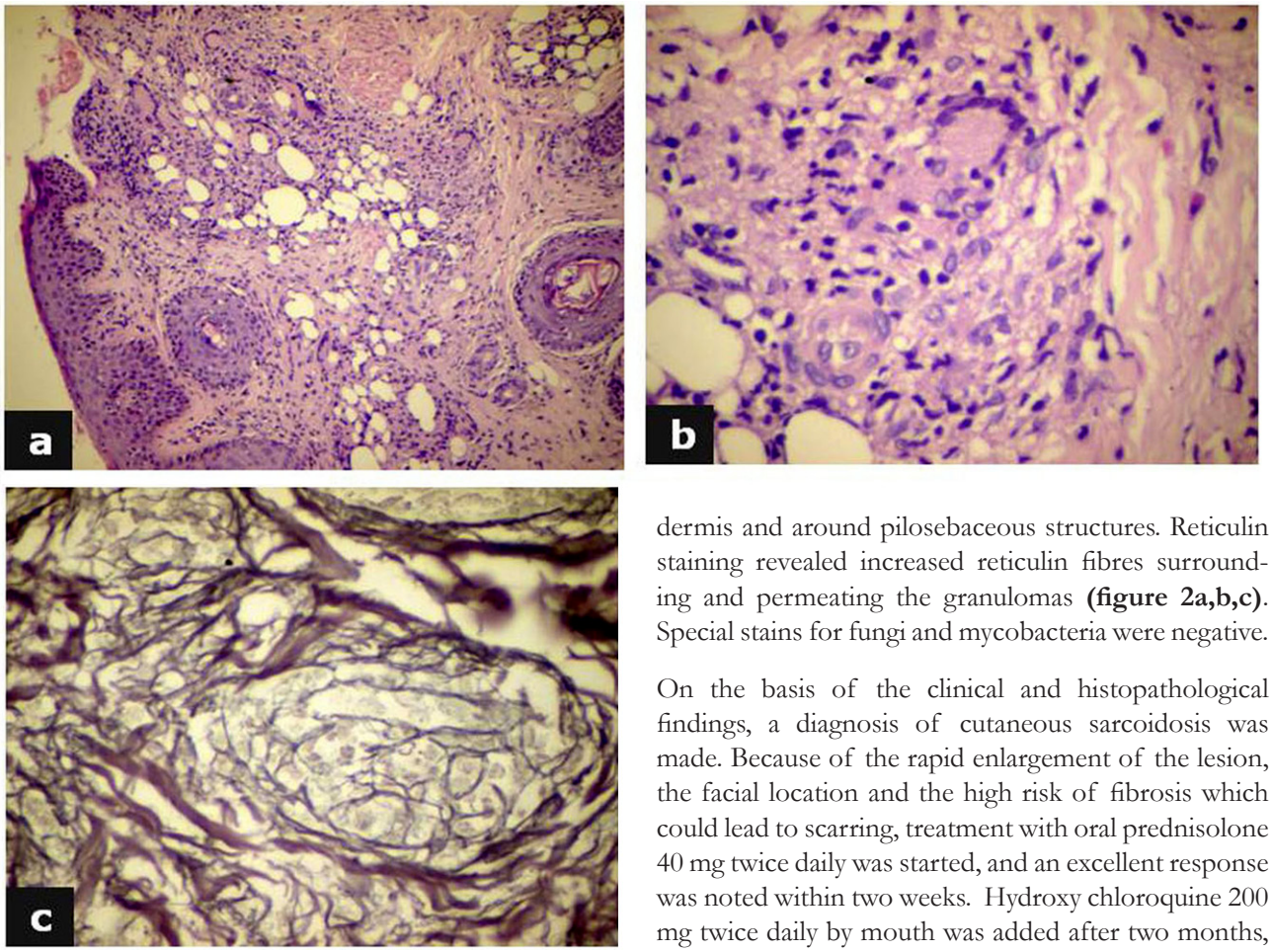

Figure 2. **Epithelioid granulomas in the dermis and around pilosebaceous structures (H and E, (a) 100x, (b) 400x (c) increased reticulin fibers surrounding and permeating the granuloma (reticulin stain 400x)**

A complete hemogram, urinalysis, blood sugar and electrolytes, renal and liver function tests including serum alkaline phosphatase levels, and serum angiotensin-converting enzyme levels were all within normal limits. The serum calcium level was 8.8 mg/dL (normal range 8.9-10.1 mg/dL for women above 19 years) and 24-hour urinary calcium excretion was 145.5 mg (normal range: 100-240 mg/24 hours). A complete antinuclear antibody profile, Mantoux test, VDRL, antibody tests for HIV, hepatitis B and C, ear lobe and slit skin smears for acid-fast bacilli were all negative. A chest disease consultation was done, and showed no abnormal clinical lung signs. An electrocardiograph, chest X-ray, pulmonary function tests, high-resolution computed tomography scan of the chest and magnetic resonance imaging of the brain revealed no abnormalities. A radiograph of both hands was normal. Neurology and ophthalmology consultations revealed no involvement of the brain or eye.

A skin biopsy from the lesion showed epithelioid granulomas with Langhan's giant cells, throughout the dermis and around pilosebaceous structures. Reticulin staining revealed increased reticulin fibres surrounding and permeating the granulomas **(figure 2a,b,c)**. Special stains for fungi and mycobacteria were negative.

On the basis of the clinical and histopathological findings, a diagnosis of cutaneous sarcoidosis was made. Because of the rapid enlargement of the lesion, the facial location and the high risk of fibrosis which could lead to scarring, treatment with oral prednisolone 40 mg twice daily was started, and an excellent response was noted within two weeks. Hydroxy chloroquine 200 mg twice daily by mouth was added after two months, and tapering the dose of corticosteroid by 10 mg every month was attempted. However, reducing the dose below 10mg per day produced an immediate flare-up and over the ensuing 18 months, she was maintained on the same dose with regular monthly followup. In addition, topical and intralesional corticosteroids in the form of 0.05% clobetasol proprionate cream once daily and 1% triamcinolone acetonide at three-weekly intervals respectively, were administered but discontinued after two months as the patient reported only a temporary minimal response.

The patient presented in July 2015 with fever, night sweats, cervical lymphadenopathy and oral ulcers of a week's duration. On examination, there was tenderness in the hypochondrium with hepatosplenomegaly. A complete blood cell count revealed a total leucocyte count of $25x10^3/\mu L$, haemoglobin 7.4g/dL and platelet count $8x10^3/\mu L$ with a normal differential count. Other laboratory tests including a complete metabolic panel, urinalysis, serology for viral infections and screening tests for haemorrhagic disease were within normal limits.

The peripheral blood smear showed leucocytosis with 78% large atypical cells. A bone marrow aspirate

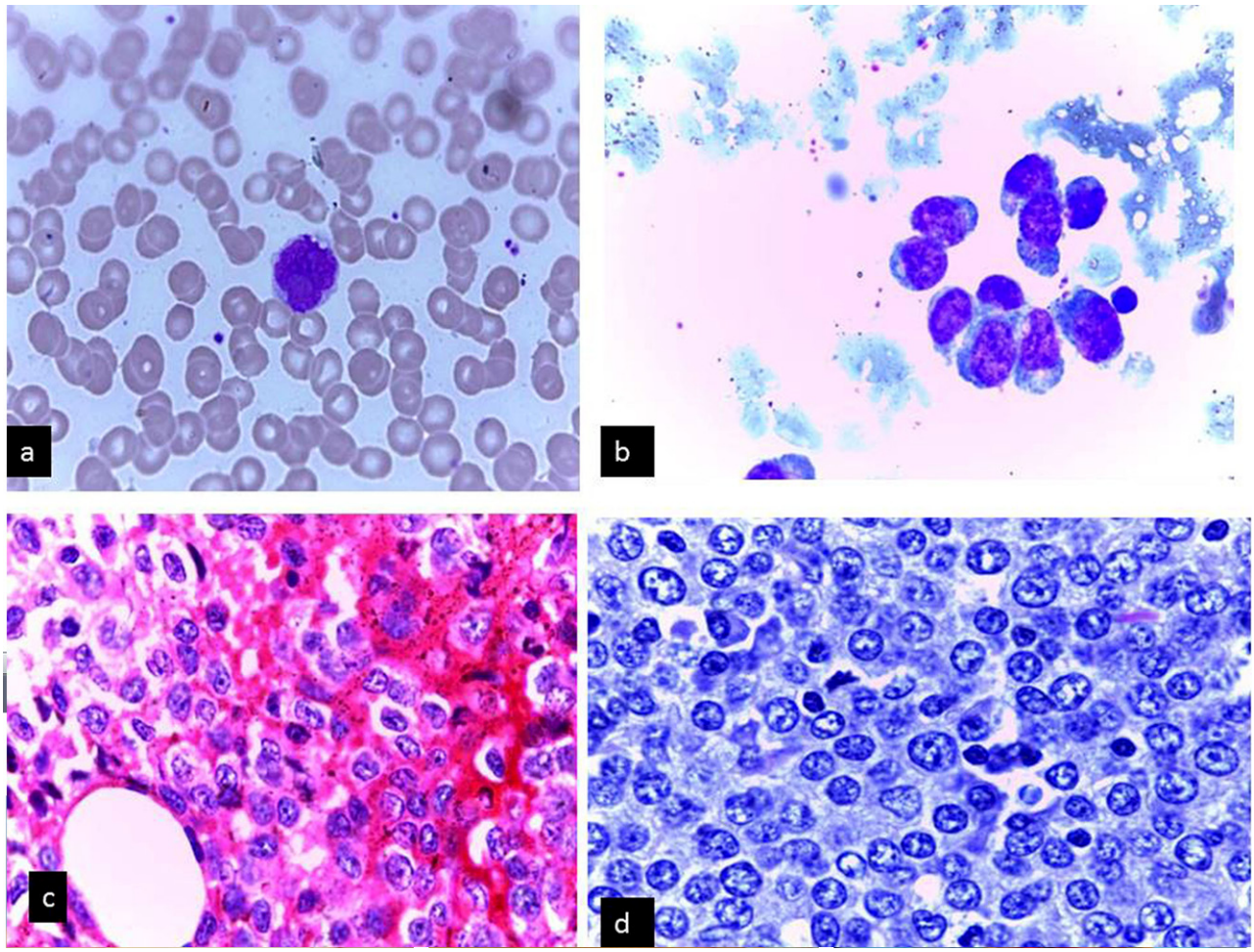

Figure 3. **(a) Large atypical cells with blast morphology in peripheral smear (Leishman stain 1000x) (b) blasts in bone marrow aspirate imprint with high nuclear/cytoplasmic ratio, open dispersed chromatin and inconspicuous nucleoli (Leishman stain 1000x) (c) blasts in trephine biopsy with round to oval nuclei, open chromatin and prominent nucleoli in some cells (H and E 400x) (d) lymph node entirely replaced by diffuse infiltration of leukemic cells (H and E 400x)**

imprint revealed a cellular marrow with predominant blast cells, which were myeloperoxidase positive. A trephine biopsy showed marrow spaces packed with cells, predominantly blasts, with all other haemopoetic series being markedly suppressed, consistent with leukemic infiltrates **(figure 3a,b,c).** An Ultrasonogram of the soft tissue of the neck revealed multiple enlarged cervical lymph nodes. A cervical lymph node biopsy showed acute monoblastic leukemic cells infiltrating the lymph nodes **(figure 3,d).** The cells were positive for CD56, CD68, CD99 **(figure 4)** and myeloperoxidase, and negative for CD3, CD20, CD15 and CD34, consistent with a myeloid cell leukaemia.

An abdominal Ultrasonogram revealed hepatomegaly and bulky kidneys with peripancreatic and retroperitoneal lymph nodes suggestive of infiltrates. Contrast enhanced computed tomography of the abdomen and pelvis showed hepatomegaly with multiple mesenteric and para-aortic lymphadenopathy.

Intriguingly, though chloroquine and steroids were stopped after admission, the lesions on the face showed a dramatic resolution (figure 5). A repeat skin biopsy showed a slightly atrophic epidermis with follicular plugging, and moderate amounts of perivascular and peri adnexal lymphocytic infiltration in the dermis, indicating regression of the initial skin lesion.

With a diagnosis of acute myeloid leukaemia, the patient was transferred to the haematology ward and the induction phase of chemotherapy was started immediately, with 213mg of intravenous cytosine arabinoside and 65mg of duanorubicin in normal saline for three days, followed by cytosine arabinoside for seven days. In spite of aggressive therapy, her general condition rapidly worsened and she died ten days later.

DISCUSSION

A significant coexistence of sarcoidosis with cancer has been noted, varying from a five-fold[2] to a 40%[3] increase, in reports as early as 1917upto 2015.[4] The most frequently occurring malignancies are Hodgkins

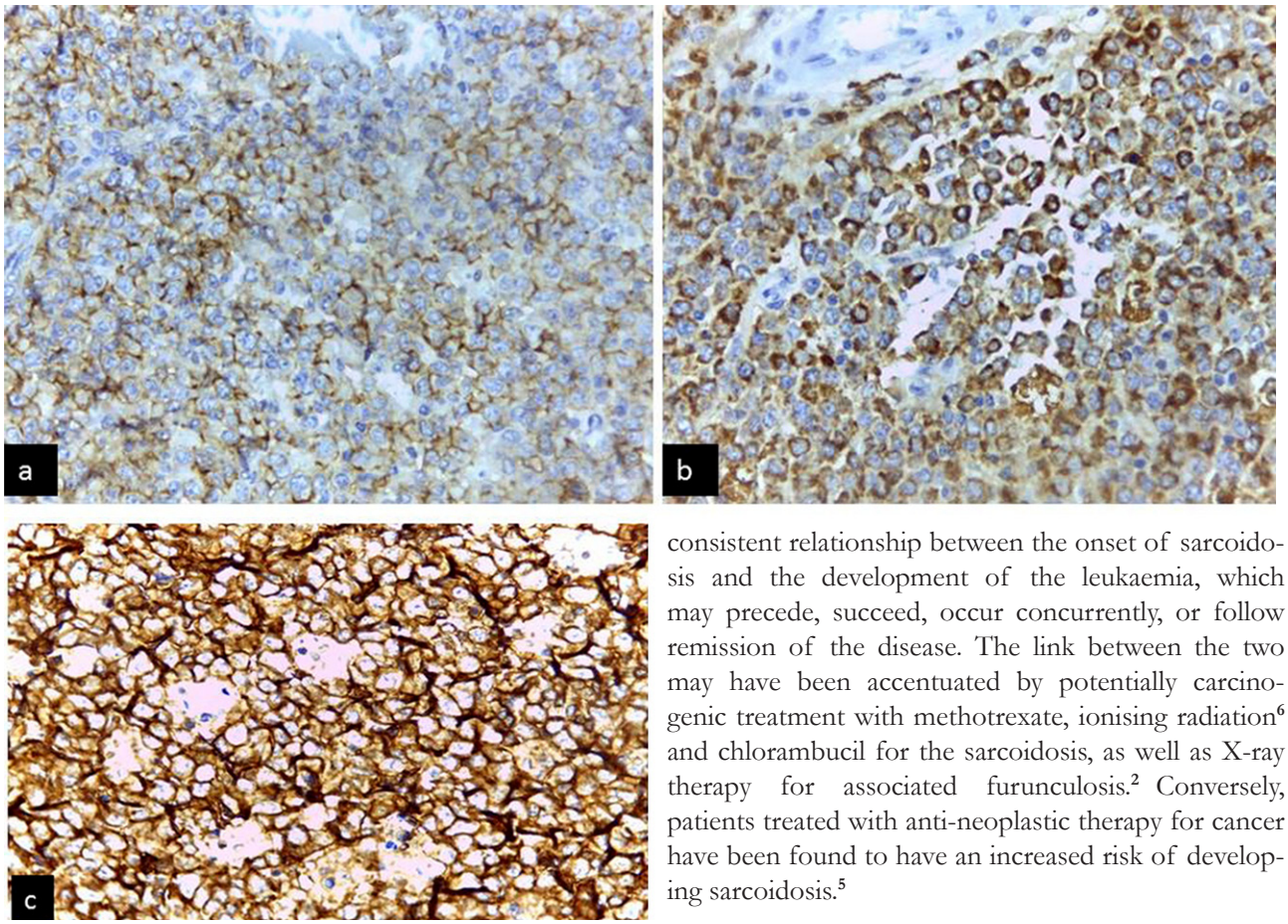

Figure 4. **Immunohistochemistry of bone marrow positive for (a)CD56 (b) CD68 (c) CD99 (immunohistochemical stain 1000x)**

disease and other lymphomas including mycosis fungoides, as well as solid organ cancers especially of the lung,[3] and skin cancers, namely squamous cell carcinoma[3] and melanoma.[4] Haematological malignancies associated with sarcoidosis constitute 73% of cases[1] and besides lymphomas, include acute myeloid leukaemia, chronic myelomonocytic leukaemia, hairy cell leukaemia, multiple myeloma,[1] and chronic lymphocytic leukaemia.[5]

With regard to acute myeloid leukaemia, there is no consistent relationship between the onset of sarcoidosis and the development of the leukaemia, which may precede, succeed, occur concurrently, or follow remission of the disease. The link between the two may have been accentuated by potentially carcinogenic treatment with methotrexate, ionising radiation[6] and chlorambucil for the sarcoidosis, as well as X-ray therapy for associated furunculosis.[2] Conversely, patients treated with anti-neoplastic therapy for cancer have been found to have an increased risk of developing sarcoidosis.[5]

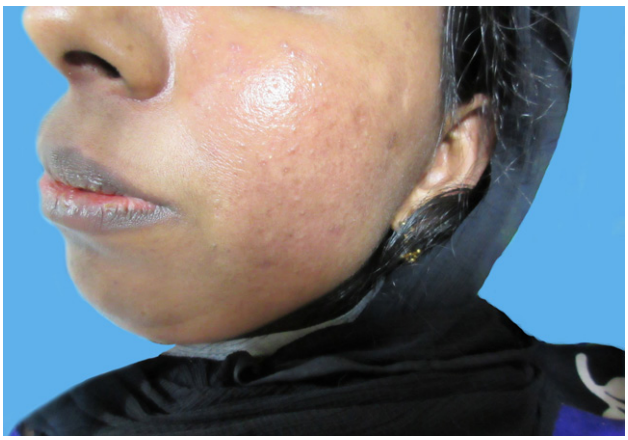

Figure 5. **Regressing lesion after development of the leukaemia**

The widespread granulomatous inflammation seen in sarcoidosis associated with an increase in the T4/T8 ratio, especially activated CD4+ T helper cells. There is a hyperactivity of the Th1 subset with a greatly increased secretion of TNF-α and IFN-γ. In patients with sarcoidosis, the regulatory T cells (Treg subset) inhibit the proliferation and secretion of IL-2 but are incapable of suppressing TNF-α and IFN-γ, whereas in normal subjects they suppress the secretion of all three cytokines. The paradoxical suppression of immune responses to various antigens (anergy) despite the intense inflammation and cytokine production could be explained by this imbalance between the effector and T reg cells.[7] A Treg survival defect has also been demonstrated, with increased Treg apoptosis.[8] The upregulation of TNF-α may be responsible for the escape from tumour immune surveillance which may be responsible for the widespread occurrence of tumour antigens seen in leukaemia. The development of cancer due to the chronic inflammation and altered immune function may be enhanced by genetic factors and immunosuppressive therapy.[9]

Malignancies associated with sarcoidosis do not necessarily affect older patients,[2,3] as demonstrated in our case. The surprising resolution of the skin sarcoidosis after the development of the leukaemia is difficult to

explain. The frequency of cutaneous lesions in patients with sarcoidosis is 20 to 25%, and in patients with cancer-associated sarcoidosis is 56.4%.[1] Sarcoidosis of the skin is important because it may be the first or only manifestation of the disease.[10] In addition, the skin is the most visible and accessible site for early diagnosis. Therefore, periodic evaluation for possible malignancy must be considered in a patient presenting with seemingly innocuous cutaneous sarcoidosis.

END NOTE

Author Information

1. Dr Manikoth Payyanadan Binitha, MBBS, DVD, MD, Former Professor and Head, Department of Dermatology and Venereology, Government Medical College, Kozhikode, Kerala.
2. Dr Anza Khader, MBBS, MD, DNB, MNAMS Associate Professor, Department of Dermatology and Venereology, Government Medical College, Kozhikode, Kerala
3. Dr Mohamed Shaan, MBBS, MD, DNB, MNAMS Additional Professor, Department of General Medicine, Government Medical College, Manjeri, Kerala. India
4. Dr Ahmed Nadeem, MBBS, MD Assistant Surgeon, Kannur, Kerala

Conflict of Interest: None declared

Acknowledgement: We gratefully acknowledge the kind assistance of Dr.Hazeena C, Associate Professor, Department of Pathology, Government Medical College, Kozhikode.

Sources of support: Nil

REFERENCES

1. Alexandrescu DT, Kauffman CL, Ichim TE, Riordan NH, Kabigting F, Dasanu CA. Cutaneous sarcoidosis and malignancy: An association between sarcoidosis with skin manifestations and systemic neoplasia. Dermatology Online J 2011;17(1): 2
2. Brincker H. The sarcoidosis-lymphoma syndrome. Br J Cancer. 1986; 54:467–73.
3. Ji J, Shu X, Li X, Sundquist K, Sundquist J, Hemminki K. Cancer risk in hospitalised sarcoidosis patients: a follow-up study in Sweden. Ann Oncol 2009;20: 1121-6.
4. Beutler BD, Cohen PR. Sarcoidosis in Melanoma Patients: Case Report and Literature Review. Cancers 2015;7:1005-21.
5. Marruchella A, Epis R, Camerone G, Tondini M. Association between chronic lymphocytic leukemia and sarcoidosis: clinical value of bronchoalveolar lavage. Sarcoidosis Vasc Diffuse Lung Dis. 1999; 16:101-3.
6. B Williams, A Francis, S Durrant. Simultaneous presentation of sarcoidosis and acute myeloid leukaemia: Predisposition to pulmonary haemorrhage. J Clin Pathol 1994;47:672-3.
7. Miyara M, Amoura Z, Parizot C, Badoual C, Dorgham K, Trad S, et al. The immune paradox of sarcoidosis and regulatory T cells. J Exp Med. 2006; 203:359-70.
8. Broos CE, van Nimwegen M, Kleinjan A, Ten Berge B, Muskens F, In 't Veen JC, et al. Impaired survival of regulatory T cells in pulmonary sarcoidosis. Respir Res 2015; 16:108.
9. Kristinsson SY, Goldin LR, Björkholm M, Koshiol J, Turesson I, Landgren O: Genetic and immune-related factors in the pathogenesis of lymphoproliferative and plasma cell malignancies. Haematologica 2009, 94:1581-9.
10. Singal A, Vij A, Pandhi D. Post herpes-zoster scar sarcoidosis with pulmonary involvement. Indian Dermatol Online J 2014;5:77-9