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Klinefelter syndrome and cutaneous localization of diffuse large B cell lymphoma: a real connection or a casual association?

Federica Scarfì[1,3], Elisabetta Magnaterra[1,3], Simone Santini[2], Franca Taviti[1]

[1]Dermatology Unit, USL Toscana Centro-Prato Hospital, Prato, Italy
[2]Hematology and Oncohematology Unit, USL Toscana Centro-Prato Hospital, Prato, Italy
[3]Section of Dermatology, Department of Health Sciences, University of Florence, Florence, Italy

Corresponding author:
Federica Scarfì,MD
Dermatology, UOSD Dermatologia, USL Toscana Centro-Prato Hospital
Piazza Ospedale, 5, 59100 Prato, Italy.
Mail: scarfif@gmail.com.
Phone: +390574 807330

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Abstract
Diffuse large B cell lymphoma (DLBCL) is a frequent aggressive subtype of non-Hodgkin lymphoma, representing nearly 30-40% of all cases. The skin may be affected by the disease either primarily or secondarily. Herein we report a clinical and dermoscopic case of skin metastasis of DLBCL in a patient with Klinefelter Syndrome.

Case Report
A 54-year-old man was consulted in January 2022 for the presence of a painless, rapidly enlarging nodule on his right axilla cavity. Clinical examination revealed a well-circumscribed, red, polypoid nodule measuring about 7 mm x 5 mm (Figure 1). The dermoscopic examination showed linear and branching vessels distributed throughout the nodule on a pink background with multiple white structureless areas (Figure 2).
His past medical history was remarkable for Klinefelter syndrome (KS) currently on testosterone replacement therapy. Furthermore, the patient had been diagnosed with DLBCL in April 2020 with multifocal bone, pleural, splenic, and lymph node metastases at the time of the diagnosis (Ann Arbor stage IVA). However, at the end of August 2020, after receiving six courses of chemotherapy with R-CHOP (cyclophosphamide, adriamycin, vincristine and prednisone plus local radiation), the patient finally achieved complete remission according to the interim response evaluation by PET-CT. The lesion was excised and sent for histopathological examination. Microscopic examination showed massive infiltration of atypical lymphoid B-cells. Immunohistochemical staining demonstrated CD-20 (+), CD-10 (+/-), bcl-6 (+), bcl-2 (+), CD-5 (-), CD-3 (-), CD-23(-), c-myc (−), consistent with the diagnosis of DLBCL skin metastasis. The fraction of Ki-67-positive lymphoid cells was 80%.

Discussion
Diffuse large B cell lymphoma (DLBCL) is a frequent aggressive subtype of non-Hodgkin lymphoma (NHL), representing nearly 30–40% of all cases[1,2]. KS is a common constitutional chromosomal disorder and the most common genetic cause of human male infertility[3], with an estimated prevalence of 1 in 650 males[4].
In almost 80-90% of KS cases, the defining karyotype is 47,XXY, while the remaining 10-20% have higher-grade chromosome aneuploidies , various grades of mosaicism or structurally abnormal X chromosomes[4].
According to some recent reports, individuals with KS would have a higher risk of developing specific types of neoplasms such as germ cells tumour and breast cancer, while the overall cancer risk appears to be the same for the general male population[5,6].
Little has been written about haematological malignancies in patients affected by KS. An increased risk of NHL has been described in KS patients[7,8]. However, the underlying mechanisms linking these two conditions are yet to be clarified.
A possible explanation lies in the higher frequency of gene fusion and/or translocation during cell division in people with chromosome aneuploidies. In particular, the increased number of chromosomes in cells may lead to the formation of chromosomal rearrangements and oncogenes activations, as already hypothesized in patients with Down's syndrome[9].

Conclusions
As far as we know, this is the first reported case of skin metastasis of DLBCL in a patient with Klinefelter Syndrome. Furthermore, our case highlights some dermoscopic findings that may address the clinical identification of DLBCL skin metastasis. Except for mycosis fungoides, limited data about dermoscopy of cutaneous lymphomas are available and essentially none about skin metastases. Two recent articles[10,11] pointed out that unfocused linear vessels with branches and focal white and orange structureless areas are frequent findings in the case of primitive cutaneous lymphoma (either B-cell or T-cell). All these features, excluding orange areas, were also observable in our case.

Obviously, a certain diagnosis of skin metastasis of DLBCL can only be achieved by performing a biopsy and histological examination. However, we believe that clarifying the connection between KS and DLBCL could facilitate early diagnosis and expedite the starting of therapies.

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Figure 1: Clinical image of the rapid enlarging red, polypoid nodule measuring about 7 mm x 5 mm located in the right axilla cavity.

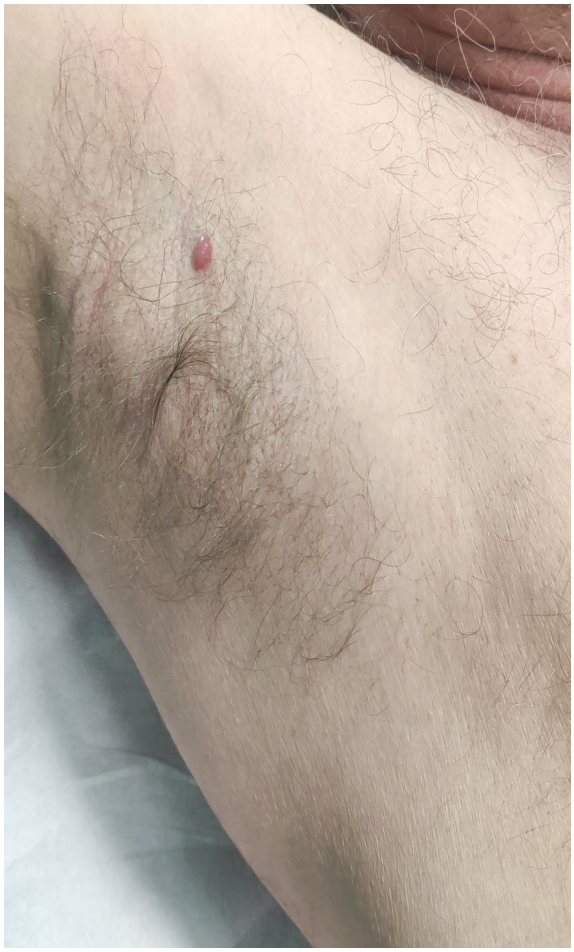

Figure 2: Dermoscopic image of the nodule shows linear and branching vessels distributed throughout the nodule on a pink background and white structureless areas.