Acral Lentigines, Is it a Paraneoplastic Syndrome?

Saad Al Mohizea and Amal Al-balbeesi
Department of Dermatology, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia

Abstract: We report a 34 years old gentleman who was referred to us with multiple brown spots on the palms, soles and scalp. He had those three months prior to being diagnosed with non-Hodgkin's lymphoma. His past history includes both Evan's syndrome and membranoproliferative glomerulonephritis treated by mycophenolate mofetil (MMF). On examination he had multiple brownish macules over the palms, soles and scalp. Biopsy from one of the lesions on the palms showed pigmentation of the basal cell layer with increased melanocytes. His lentigines are most likely induced by immunosuppression due to Non-Hodgkin's lymphoma.

Key words: paraneoplastic syndromes, acral lentigines, malignancy.

Correspondence: Saad Al Mohizea
King Saud University, Department of Dermatology
P.O. Box 7805
Riyadh 11472 Saudi Arabia
E-mail address: rodomani@yahoo.com
Introduction
Paraneoplastic dermatosis may represent the first finding that a malignancy is lurking, if not presenting simultaneously. These interesting signs may increase the likelihood that the patients will survive, but only if recognized early on, by the curious dermatologist.\textsuperscript{(1)}

Acral lentigines have been linked recently to malignancy.\textsuperscript{(2,3)} We present this case as a possible example of a paraneoplastic syndrome which for the first time is shown to predate malignancy.

Case Scenario
Our patient is a 44 years old gentleman of Middle Eastern origin whose Fitzpatrick’s skin type is IV and who has never complained of excessive freckling or skin problems. He has Evan’s syndrome which was diagnosed since childhood with recurrent episodes of hemolytic anemia. He was also diagnosed with membranoproliferative glomerulonephritis for which he was treated with mycophenolate mofetil (MMF).

Three months before he was diagnosed to have non-Hodgkin’s lymphoma, he noticed brown spots spreading rapidly from his palms to his soles and finally to the scalp as seen in Fig. 1 and Fig. 2. He later sustained right femur fracture and was admitted. Since his lesions were suspicious, He was seen by an oncologist and after his extensive work up he was diagnosed with Non-Hodgkin’s lymphoma after it was confirmed by bone marrow biopsy. He was started on R-CHOP chemotherapy and had already received three cycles when he was referred to us. The patient noticed that his lentigines got darker and more numerous with chemotherapy.

On examination he had multiple brownish round macules averaging 3 mm in size on his palms, soles and scalp. They were asymptomatic and other body parts were not affected including his oral mucosa and genitalia. There was no similar illness in the family. Biopsy taken from one of the lesions over the palm showed pigmentation of the basal cell layer with increased melanocytes.

Discussion
There is a plethora of evidence linking immunosuppression and malignancy to eruptive nevi.\textsuperscript{(4)} but with acral lentigines the evidence is scanty. In addition to the five cases reported as paraneoplastic,\textsuperscript{(2,3)} acral lentigines have been reported in two patients with HIV.\textsuperscript{(5)} It’s not clear why this happens. Many factors are incriminated. UV exposure\textsuperscript{(6)} and dysregulation of certain growth factors during re-epithelialization\textsuperscript{(7)} may explain some types of eruptive nevi. But more pertinent to our case, immunosuppression seems to be the main cause.\textsuperscript{(8)} This could be from the chemotherapy or the disease itself, since it has been shown that some malignancies induce immunosuppression like in breast cancer.\textsuperscript{(9)} Finally, UV exposure has been shown to induce immunosuppression too.\textsuperscript{(10)}

Only recently, five cases of Acral lentigines were linked to malignancy. The first patients had acral lentigines occurring simultaneously with large cell lymphoma of the small bowel before starting chemotherapy. The second patient had breast cancer and presented with acral lentigines only after radiotherapy and surgery was performed. In The last three patients the onset of the lentigines was either not mentioned or unknown. They had adenocarcinoma of the stomach, breast cancer and melanoma.\textsuperscript{(12)}

In our case, the patient had lentigines before he was diagnosed to have non-Hodgkin’s lymphoma. This maybe a true paraneoplastic syndrome presenting before malignancy, or he might have been ill from the beginning, having a silent malignancy. It's noteworthy that some authors consider true paraneoplastic syndromes only when they present after malignancy and parallel its course.\textsuperscript{(11)} However, pruritus a well known cutaneous manifestation of lymphomas and leukemias are known to precede malignancy in some occasions.\textsuperscript{(12)}

One can argue that the evidence is both thin and circumstantial. Indeed, only six cases including ours are thought to be paraneoplastic syndromes. However, the incidence of paraneoplastic syndromes is uncommon to rare.\textsuperscript{(11)} The unique localization of lentigines to acral sites (and scalp) points to a specific insult. Moreover the temporal relationship between lentigines and the malignancies occurring before, during and after is crucial evidence. Our patient has skin type IV, he has never experienced widespread lentigines before and presented with this only in his forties. Such presentation must have been the result of a new insult.

Evans syndrome is an uncommon condition defined by the combination of immune thrombocytopenia and autoimmune hemolytic anemia with a positive direct antiglobulin test in the absence of known underlying etiology.\textsuperscript{(13)} Non-Hodgkin’s lymphoma has been associated with Evans
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References


syndrome. [14] Acral lentigines are unlikely to be due to Evans syndrome in our patient since he had the syndrome since childhood. Likewise, since the patient was already on mycophenolate mofetil for two years, it’s unlikely that the lentigines are caused by it.

Nevertheless, even if acral lentigines develop or worsen after chemotherapy, this supports the notion that immunosuppression is the common denominator between malignancy, chemotherapy/MMF and HIV. To complete the puzzle, it is helpful to know the prevalence of acral lentigines in normal population. Besides malignancy and HIV, Acral lentigines have been associated with PUVA[15] and cerebral vascular accidents.[16]

In summary, the sudden eruption of lentigines over palms, soles and scalp may signal a hidden malignancy and should alert the physician to look for silent neoplasms. However, more studies are needed to confirm this association.

![Fig. (1). Lentigines on the right palm.](image1)

![Fig. (2). Lentigines on the scalp.](image2)