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Ph: (956) 971 - 0404
www.oasisderm.com

Acral Lentiginous Melanoma

Acral lentiginous melanoma (ALM) is a rare subtype of cutaneous malignant melanoma that predominantly affects the hands and feet, particularly the palms, soles, and subungual (under-nail) areas. Unlike most melanoma types that typically arise in sun-exposed areas, ALM occurs in non-sun-exposed regions, making its pathogenesis and clinical presentation distinct. This melanoma subtype is characterized by a wide variety of colors and morphologies, including both pigmented and amelanotic forms. Although rare, ALM is the most common type of melanoma in individuals with darker skin tones, such as those of African, Asian, and Hispanic descent.

Clinical Presentation and Risk Factors

The clinical presentation of ALM varies greatly, making its diagnosis challenging. In its most common form, ALM presents as a flat, brown, gray, or black lesion with irregular borders. However, the amelanotic variant, which lacks dark pigmentation, can present as a red-to-pink macule, papule, plaque, or nodule. Regardless of pigmentation, ALM most frequently occurs on the lower extremities, particularly on the big toe, but can also develop on the palms and under nails. Delayed diagnosis is a frequent issue due to the location of ALM, as areas like the bottom of the feet and subungual regions are less likely to be regularly inspected, and biopsies may be avoided due to concerns about impairing daily activities. In advanced stages, ALM lesions may become ulcerated, eroded, inflamed, and itchy, further complicating clinical evaluation.

The mean age of presentation is between 50 and 60 years, and the incidence is generally similar between men and women. Although ALM can affect individuals of any race or skin type, it is notably more prevalent in those with darker skin, which suggests that genetic and environmental factors may play a role in its development. Notably, ALM does not usually present on sun-exposed skin, differentiating it from other types of melanoma that are strongly associated with ultraviolet (UV) exposure. The most widely accepted risk factors for ALM include repeated trauma, friction, maceration, and irritation in the affected areas. These factors may contribute to the development of malignant tissue growth, but a definitive cause for ALM remains unclear.

Genetic Mutations and Pathogenesis

Acral lentiginous melanoma has been found to harbor mutations in various genes that contribute to its aggressive behavior. Notably, mutations in the KIT, BRAF, NRAS, NF1, and GNAQ genes have been identified in tissue profiling of ALM cases. These mutations are thought to promote tumor progression, with KIT mutations, in particular, being highly prevalent in ALM, distinguishing it from other melanoma subtypes. The presence of these mutations, particularly in the absence of UV

exposure, underscores the unique molecular profile of ALM and its distinct pathogenesis compared to other melanomas.

Diagnosis

Due to the often subtle clinical presentation and the challenges of inspecting non-sun-exposed areas, the diagnosis of ALM is typically delayed. Initial diagnosis is primarily clinical, with dermoscopy serving as an essential tool for evaluating suspicious lesions. Dermoscopy, which uses magnification to visualize skin lesions in greater detail, can help differentiate ALM from other skin conditions and early melanomas. If a lesion appears suspicious for melanoma, a biopsy is necessary to confirm the diagnosis and assess the histological features.

Histologically, ALM is characterized by confluent single-cell melanocytic proliferation along the dermo-epidermal junction with pagetoid spread, which can be identified in a biopsy sample. The depth of invasion and the presence of mitotic figures are important indicators of tumor aggressiveness. Due to the aggressive nature of ALM and its potential for metastasis, staging and thorough evaluation of regional lymph nodes are critical components of the diagnostic workup.

Treatment Options

Surgical excision remains the primary treatment for ALM, and the goal is complete removal of the tumor with clear margins to reduce the risk of recurrence. The width of surgical margins depends on the depth of invasion, with more extensive margins required for tumors that invade deeper into the skin. In cases where the melanoma has spread to the lymph nodes or distant organs, additional treatments are necessary.

Recent advances in the treatment of metastatic ALM include immunotherapy and targeted therapy. Immunotherapy, particularly immune checkpoint inhibitors, has revolutionized the management of metastatic melanoma. Drugs that target CTLA-4 (e.g., ipilimumab) and PD-1 (e.g., pembrolizumab and nivolumab) have shown significant efficacy in improving progression-free survival in patients with advanced melanoma, including ALM. These therapies work by enhancing the body's immune response to melanoma cells.

Targeted therapy, which aims to inhibit specific molecular drivers of melanoma, is also a promising treatment for ALM, particularly in patients with BRAF mutations. BRAF inhibitors (e.g., vemurafenib and dabrafenib), often used in combination with MEK inhibitors (e.g., trametinib), have shown effectiveness in treating ALM with BRAF mutations and can improve survival rates.

Prognosis

The prognosis of ALM is generally poor due to its tendency to present at advanced stages and its aggressive nature. The delay in diagnosis often leads to late-stage presentation, which is associated with lower survival rates. However, the prognosis can vary depending on the stage of the disease at

diagnosis, the presence of lymph node involvement, and the molecular characteristics of the tumor. The identification of mutations in genes like KIT and BRAF may also influence treatment response and long-term outcomes. With advances in immunotherapy and targeted therapies, the prognosis for patients with metastatic ALM has improved, though it remains a challenging malignancy to treat.

Conclusion

Acral lentiginous melanoma is a rare and aggressive form of melanoma that presents unique diagnostic and therapeutic challenges. Its occurrence on non-sun-exposed areas, such as the palms, soles, and under nails, and its ability to metastasize early, make it difficult to detect and treat. However, with advances in diagnostic techniques, such as dermoscopy, and the development of targeted therapies and immunotherapies, the management of ALM has improved significantly. Early detection and treatment remain crucial in improving the prognosis for patients with this rare form of melanoma.

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