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A Rare Case of Paraneoplastic Raynaud's Phenomenon and Uveal Melanoma

Lara Vasari[1], Sanda Špoljarić Carević[1], Lucija Tomić Babić[1], Marija Bakula[2]

[1]Special Hospital for Medical Rehabilitation Naftalan, Ivanić-Grad, Croatia; [2]University Hospital Center Zagreb, Zagreb, Croatia

Corresponding author:
Sanda Špoljarić Carević, MD
Special Hospital for Medical Rehabilitation Naftalan,
Ivanic Grad,
Croatia
ssanda1977@gmail.com

ABSTRACT Raynaud's phenomenon (RP) presents as acral skin pallor, cyanosis, and erythema, usually after cold exposure or emotional stress. Symptoms of RP affect 3-5% of the general population, with the incidence four times higher in women than in men. Paraneoplastic RP is extremely rare and is thought to involve plasma hyperviscosity and blood hypercoagulability, which are present in patients with malignant diseases. Paraneoplastic RP often presents abruptly and, besides changes in skin color, it includes erosions, ulcerations, and necrosis, resulting in severe pain. We present a case of a 62-year-old female patient who suddenly developed symptoms of RP, characterized by periodic skin pallor without erosions or associated pain in all fingers, lasting 10-15 minutes after cold exposure. She was diagnosed with uveal melanoma three months prior and was also in a 14-year remission from invasive ductal carcinoma. Investigations confirmed positive antinuclear antibodies (ANA) with PCNA (proliferating cell nuclear antigen) and myositis-specific antibodies including anti-Jo, anti-mitochondrial antibody (AMA-M2), and anti-benzylpenicilloyl antibody (BPO).

KEYWORDS: Raynaud's phenomenon, uveal melanoma, paraneoplastic syndrome

Raynaud's phenomenon (RP) affecting 3-5% of the general population with an incidence rate approximately four times higher in women than in men, can manifest as primary, occurring in healthy individuals, or as secondary, associated with autoimmune, hematological, endocrinological and vascular diseases, or cancers (1). According to our knowledge, this paper presents the first case of paraneoplastic RP preceding uveal melanoma.

A 62-year-old female patient presented to the clinic in March 2022 due to two years periodic pallor of the skin without erosions and with accompanying pain in all fingers, predominantly in the third finger of the right hand, lasting 10-15 minutes after exposure to cold. (Figure 1.) In 2008, the patient was diagnosed with invasive ductal carcinoma of the right breast (pT1cN0M0, ER 0%, PgR 0%, HER 2 0). She underwent superior segmentectomy with axillary evacuation, followed by adjuvant chemotherapy consisting of six cycles of doxorubicin and cyclophosphamide, along with radiotherapy. The patient has been in remission after the treatment. Upon presentation of RP in 2022, the condition was confirmed by capillaroscopy, telethermography, and cryoactivation. Complete blood count and inflammatory parameters were normal, with normal values of creatine kinase (CK) and lactate dehydrogenase (LDH), no consumption of complement, and unremarkable serology for hepatitis B and C. Positive antinuclear antibodies (ANA) were found along with proliferating cell nuclear antigen (PCNA), and myositis-specific antibodies anti-Jo, anti-mitochondrial antibody (AMA-M2), and anti-benzylpenicilloyl antibody (BPO). Serological findings suggested a systemic autoimmune disease, specifically myositis, but the patient was clinically without symptomatology and therefore did not meet enough criteria for the diagnosis of inflammatory myositis or another systemic connective tissue disease. Therapy with

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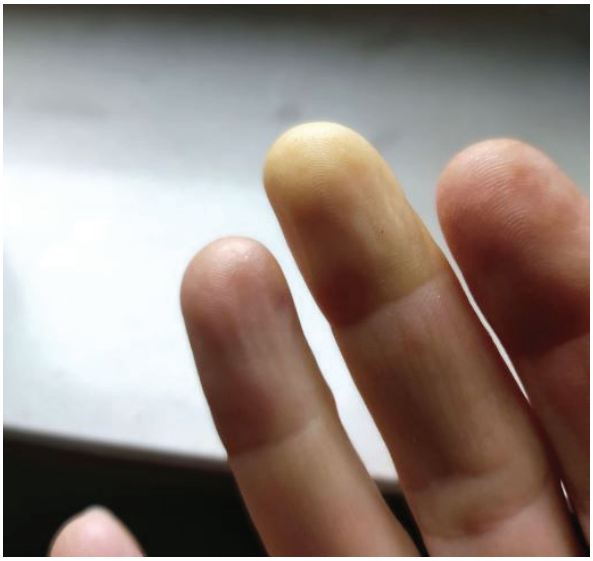

Figure 1. Raynaud's phenomenon

Pallor of the skin predominantly in the third finger of the right hand.

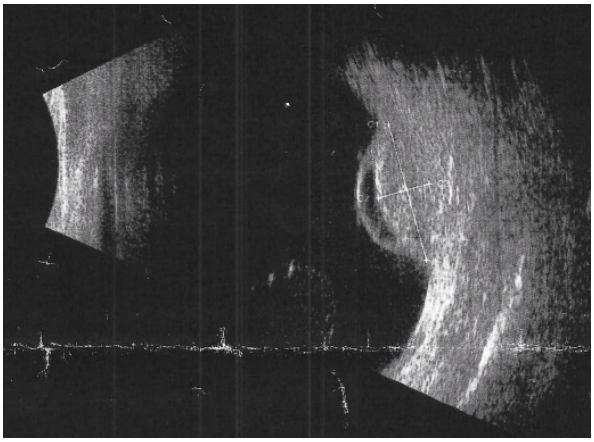

Figure 2. Ultrasound image of both eyes

In the posterior pole of the right eye, a solid domed protrusion of the retina which corresponds to uveal melanoma.

nifedipine 10 mg in the evening was introduced, stabilizing the symptoms of Raynaud's phenomenon.

In December 2021, the patient had a feeling of discomfort and a haze in the right eye, and after an ophthalmological examination, a uveal melanoma of the right eye was diagnosed (figure 2), for which she was treated with gamma knife therapy.

The paraneoplastic form of RP is exceptionally rare. In the etiopathogenesis of paraneoplastic RP, plasma hyperviscosity and blood hypercoagulability play an important role in patients with malignancies (1). Cases of paraneoplastic acral vascular syndrome (including RP) have been most described among adenocarcinomas, hematological malignancies, epidermoid and anaplastic carcinomas (2). According to the tumor site, the most frequent localizations are hematologic malignancies, lung, ovary, breast, and uterus (2). Paraneoplastic RP usually presents suddenly and, in addition to skin color changes, is accompanied by erosions, ulcerations, and necrosis, causing severe pain (3). Patients with paraneoplastic RP often have positive ANA, which was also the case with the presented patient (3). Vanlacker et al., linked the severity of RP symptoms and the progression or recurrence of breast cancer, describing five cases of paraneoplastic RP in patients with breast cancer (3). At the time our patient presented with RP symptoms, there was no detected progression or recurrence of breast cancer, but at the end of 2021, uveal melanoma of the right eye was discovered, and a few months later, the diagnosis of RP was established. To the best of our knowledge, to date just one case of paraneoplastic RP and metastatic skin melanoma has been described (4). In Besnerais et al.'s study, which examined 15 patients with acral ischemia and carcinoma occurring either a year before or after the initial episode of acral ischemia, one patient was diagnosed with melanoma (5). Also, Gambichler et al., presented a patient with paraneoplastic acral vascular syndrome and metastatic melanoma who was treated with immunotherapy, but in their case the role of anti-PD-1 or anti-CTLA-4 antibodies in the onset of acral vascular syndrome cannot be excluded (6). Furthermore, there is also the question of the connection between positive myositis-specific antibodies and cancer. According to Marzecka et al., in 5-40% of cases, all myositis-specific antibodies can be associated with malignant diseases (7). Idiopathic inflammatory myopathies are often associated with malignant neoplasms, among which dermatomyositis has the strongest connection. Although paraneoplastic syndrome is most commonly associated with transcriptional intermediary factor 1-γ (TIF1-γ) antibodies and nuclear matrix protein-2 (NXP-2) antibodies, the literature also describes the appearance of anti-Jo antibodies associated with malignancies, which were positive in the presented patient (8,9). The study by Hamaguchi et al., showed that precisely anti-Jo antibodies were the most frequently positive among all other antibodies in a group of patients with dermatomyositis and malignancies (60%) (10). In the mentioned group of patients, 30% had breast cancer (10).

Recognizing RP as a potential indicator of hidden malignant diseases underscores the importance of comprehensive assessment of patients with this symptom. Patients with positive myositis-specific antibodies may be at increased risk for developing malignant tumors. However, further research is needed

to confirm this association, especially in patients with RP or acral ischemia. These findings highlight the need for careful monitoring and evaluation of patients with RP for early detection and management of possible malignancies.

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