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Case report

Paraneoplastic Raynaud phenomenon associated with metastatic ovarian cancer: A case report and review of the literature

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1. Introduction

Paraneoplastic syndromes occur in approximately 8% of malignancies. While the pathogenesis is not well understood, these syndromes may be related to production of proteins, hormones, cytokines, or mediated by immune cross reactivity between the tumor and normal cells. These phenomena may be associated with a wide range of phenotypes affecting the endocrine, neurologic, rheumatologic, dermatologic, or hematologic systems (Pelosof and Gerber, 2010).

Dermatologic and rheumatologic paraneoplasias may be difficult to identify, as many of these disease processes occur in the absence of clinically overt malignancy. As such, the rheumatologic diagnoses are often made prior to the identification of a malignancy. Often, these rheumatologic diseases can be less responsive to conventional therapies than their non-paraneoplastic counterparts (Manger and Schett, 2014; Dieffenbach et al., 2018). However, paraneoplastic syndromes often improve or resolve with treatment of the underlying cancer. Identification of a rheumatologic paraneoplastic syndrome may therefore aid in earlier diagnosis of disease and may allow for earlier detection of disease recurrence.

2. Case presentation

A 56-year-old Korean female initially presented to her primary care physician with symptoms of acute pain, paresthesia, and discoloration of her fingers. She was referred to a rheumatologist, and a panel of markers for autoimmune and inflammatory disease was performed, all of which resulted within the normal range. She was diagnosed with Raynaud phenomenon and was prescribed hydroxychloroquine to help control her symptoms. When this failed to improve her symptoms after 6 weeks, several other medications were prescribed, including an angiotensin receptor blocker, amlodipine, fluoxetine, and topical nitroglycerin paste. Despite multiple medications, her symptoms continued to progress, and she sought a second opinion from another rheumatologist. At this point, she had developed digital ulcerations and was wearing gloves regularly throughout the day to keep her hands warm (Fig. 1). The second rheumatologist she saw prescribed an oral prostacyclin analogue. When this failed to improve her condition, she sought a third rheumatology opinion, now 4 months after she had presented with her initial symptoms. On further questioning, the patient endorsed symptoms of malaise, fatigue, night sweats, alopecia, and dry eyes. Her rheumatologist became concerned for an underlying malignancy and ordered a CT scan of the chest, abdomen, and pelvis, which was notable for peritoneal carcinomatosis and omental caking. A CA-125 was drawn and was markedly elevated at 862 U/mL. CEA and CA19-9 tumor markers were within normal limits. The patient was referred to gynecologic oncology and medical oncology and, now 5 months after her initial Raynaud symptoms, underwent a primary cytoreductive surgery which included exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, ileocecectomy, low anterior resection, splenectomy, and peritoneal stripping. At the completion of her surgery, she had an optimal cytoreductive effort with 2–3 mm of residual disease. She had an uneventful postoperative recovery. Approximately two weeks later, she was seen in the office for a postoperative visit. At this time, her Raynaud symptoms had significantly improved. The ulcerations of her fingers had resolved, and her subjective discomfort was much improved. Approximately 3 weeks later, she was seen again, and her

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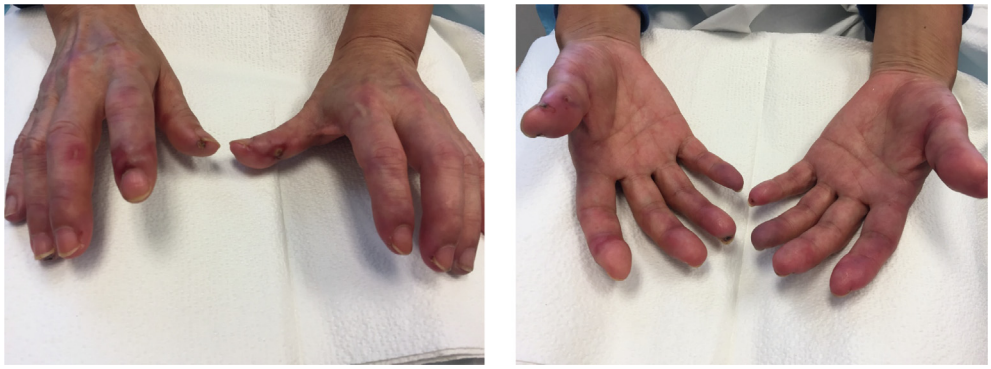

Fig. 1. Prior to the diagnosis of ovarian cancer, patient developed Raynaud's syndrome associated with digital ulcerations, which was refractory to multiple treatments.

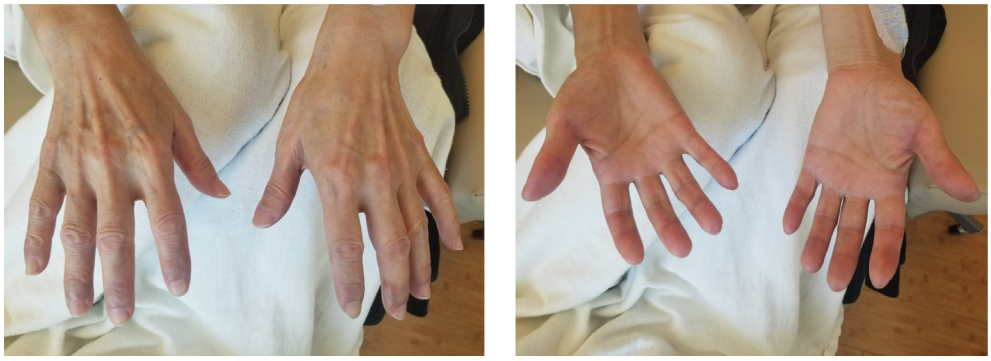

Fig. 2. Raynaud's syndrome resolved three weeks following optimal cytoreduction for ovarian cancer, prior to the initiation of chemotherapy.

Raynaud symptoms had essentially resolved, even prior to starting adjuvant chemotherapy (Fig. 2).

At the time of this report, the patient has completed six cycles of adjuvant platinum-based chemotherapy uneventfully. CA-125 has normalized (10 U/mL). Interestingly, she was found to have a germline BRCA1 mutation and will therefore be started on a maintenance poly ADP ribose polymerase (PARP) inhibitor (olaparib), which has demonstrated a significantly lower 3-year rate of progression or death (Moore et al., 2018). Her Raynaud phenomenon has remained in remission throughout her chemotherapy treatment course.

3. Discussion

Raynaud's phenomenon is a relatively common clinical disorder that affects up to 5% of the population in the United States (Maricq et al., 1997). Raynaud's phenomenon is an exaggerated normal physiologic response to cold exposure and to emotional stress. These triggers result in vasospasm of the fingers and toes, although other sites, including the tongue, nose, ears, and nipples, can also be affected (Block and Sequeira, 2001). Typically, well-demarcated pallor of the digits due to ischemia leads to cyanosis, pain, and paresthesia, followed by erythema, upon rewarming and reperfusion. The vast majority of Raynaud's phenomenon is primary, which is considered benign, idiopathic, and occurs at an earlier age in the second or third decade. On the contrary, secondary Raynaud's phenomenon often arises after 40 years of age and is diagnosed in conjunction with associated conditions, such as rheumatic diseases, hematologic disorders, occlusive vascular diseases, and rarely with malignancy. Sequelae of untreated secondary Raynaud's include digital ulceration and even critical ischemia when severe (Block and Sequeira, 2001; Herrick, 2017).

As early as 1884, severe digital ischemia was reported as an early and unusual manifestation of malignancy (O'Conner, 1884). Hawley et al. also published digital ischemia revealing an ovarian cancer in 1967 (Hawley et al., 1967). Then, Poszepczynska-Guigne et al., identified 68 previously reported cases of paraneoplastic Raynaud's phenomenon via the Medline database search, which included 6 cases of adenocarcinoma and 1 case of aplastic carcinoma of the ovary (Poszepczynska-Guigne et al., 2002). Although ovarian malignancies are not often associated with paraneoplastic syndromes, a paraneoplastic neurologic syndrome (anti-NMDA receptor encephalitis) may be rarely associated with an ovarian teratoma or adenocarcinoma. A few case reports also have illustrated the association between dermatomyositis and ovarian cancer (Cherin et al., 1993).

Our patient in this case developed an acute onset and rapidly progressive Raynaud's phenomenon, complicated by development of painful digital ulcerations at 55 years of age. Comprehensive rheumatologic workup was negative, and her condition was recalcitrant to the usual treatments of Raynaud's phenomenon, including pain control, maintaining the core body temperature and extremities warm at all times, topical vasodilators, calcium channel blockers, angiotensin receptor blockers, selective serotonin receptor blockers, and prostacyclin analogues (Herrick, 2017). Similar to other cases in the literature in which 48% of paraneoplastic Raynaud's phenomenon regressed after tumor treatment (Poszepczynska-Guigne et al., 2002), our patient's Raynaud's phenomenon resolved, and her digital ulcerations also healed rapidly following cytoreductive surgery and initiation of adjuvant chemotherapy. Legrain et al. (1999), reported a similar outcome in her patient, who underwent bilateral salpingo-oophorectomy and hysterectomy with omentectomy, followed by adjuvant chemotherapy.

In conclusion, paraneoplastic Raynaud's phenomenon associated with underlying malignancies is rare, with very few cases reported in association with ovarian cancer. Nonetheless, our case underscores the need for physicians to consider occult malignancies in the differential diagnosis when patients present with an abrupt onset of Raynaud's phenomenon. Paraneoplastic Raynaud's phenomenon should be suspected especially if other secondary workup is negative and if the

symptoms progress despite the usual treatment. In most cases, the treatment of the underlying malignancy would resolve the paraneoplastic vascular involvement, but more importantly, early detection of the underlying malignancy may lead to earlier antineoplastic treatment and potential improvement in clinical outcome.

Author contribution

T.L., M.S., and M.Z. contributed in the writing of the manuscript. D.S. assisted in editing.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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