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LETTER TO THE EDITOR

Paraneoplastic Raynaud's phenomenon associated to astrocytoma

KEYWORDS
Raynaud's phenomenon;
Paraneoplastic acral vascular syndrome;
Brain tumor;
Astrocytoma

Introduction

Raynaud's phenomenon (RP) is a type of vascular disease characterized by vasoconstriction of the cutaneous arterioles in response to provoking factors such as exposure to cold temperature or emotional stress. It can be categorized as either primary or secondary. In patients affected by primary RP, the majority of cases, no underlying disease can be detected. Conversely, secondary RP is associated with a disease, most commonly connective tissue disorders such as systemic sclerosis and systemic lupus erythematosus. Further causes include drugs, occupational diseases and endocrine disorders [1—3]. Malignancy is a rarely reported cause of secondary RP. Paraneoplastic RP has been described in patients affected by malignancy. In this report, we describe a 25-year-old woman with RP attacks that occurred before diagnosis of astrocytoma and disappeared after surgical resection of the brain mass.

Observation

A 25-year-old woman presented to our angiology outpatient clinic because in the previous ten days she had two RP attacks affecting the fifth finger of her left hand. The attacks lasted about fifteen minutes, started out with skin pallor followed by cyanosis, without subsequent reactive hyperemia. Before the second attack, the patient reported self-limiting paresthesia of the left side of upper and lower lips.

She was a student. Her past medical and family history was unremarkable. She had no known drug allergies and she was not taking medications. She did not smoke, drink alcohol and use illicit drugs.

At presentation, the patient's heart rate was 80 beats per minute, blood pressure 120/80 mmHg, respiratory rate 14 breaths per minute, oxygen saturation 99% while she was breathing ambient air and temperature 36 °C.

Physical examination showed no evidence of sclerodactyly, skin tightening, digital pits or ulcers. On peripheral vascular system examination, pulses were brisk and symmetric, bruits were absent and the Allen test was negative in both arms.

On neurological examination, she was alert and cooperative, oriented to person, place, and time. There was no evidence of muscle tone or strength abnormalities. Rapid alternating movements, finger-to-nose and heel-to-shin were intact. Gait was with normal base and deep tendon reflexes were average and symmetric with plantar response downgoing. Sensory system evaluation was notable for hypoesthesia and hypoalgesia of the left side of upper and lower lips.

Laboratory tests were within normal reference range and nailfold capillaroscopy did not show any abnormalities.

MRI of the brain was acquired using an 8-channel head coil at 1.5 T. Brain MRI showed an intra-axial mass with infiltrative behavior with irregular and ill-defined margins, located within the white matter of the left frontal lobe at the level of superior frontal gyrus. The lesion caused expansion of the surrounding cortex without any significant edema or mass effect (Fig. 1).

The patient was referred to a neurosurgeon to perform resection of the brain mass. Histopathological findings were consistent with astrocytoma. Five years after surgical removal, there was no cancer recurrence and patient denied further RP attacks.

Discussion

RP associated with malignancy was first described in 1920 by Hamilton [4], who observed a severe RP with digital necrosis in a patient with esophageal cancer. Since then, there have been reported in medical literature a lot of cases of digital ischemia, secondary or not to RP, associated with cancer. The most common associations are solid tumors of

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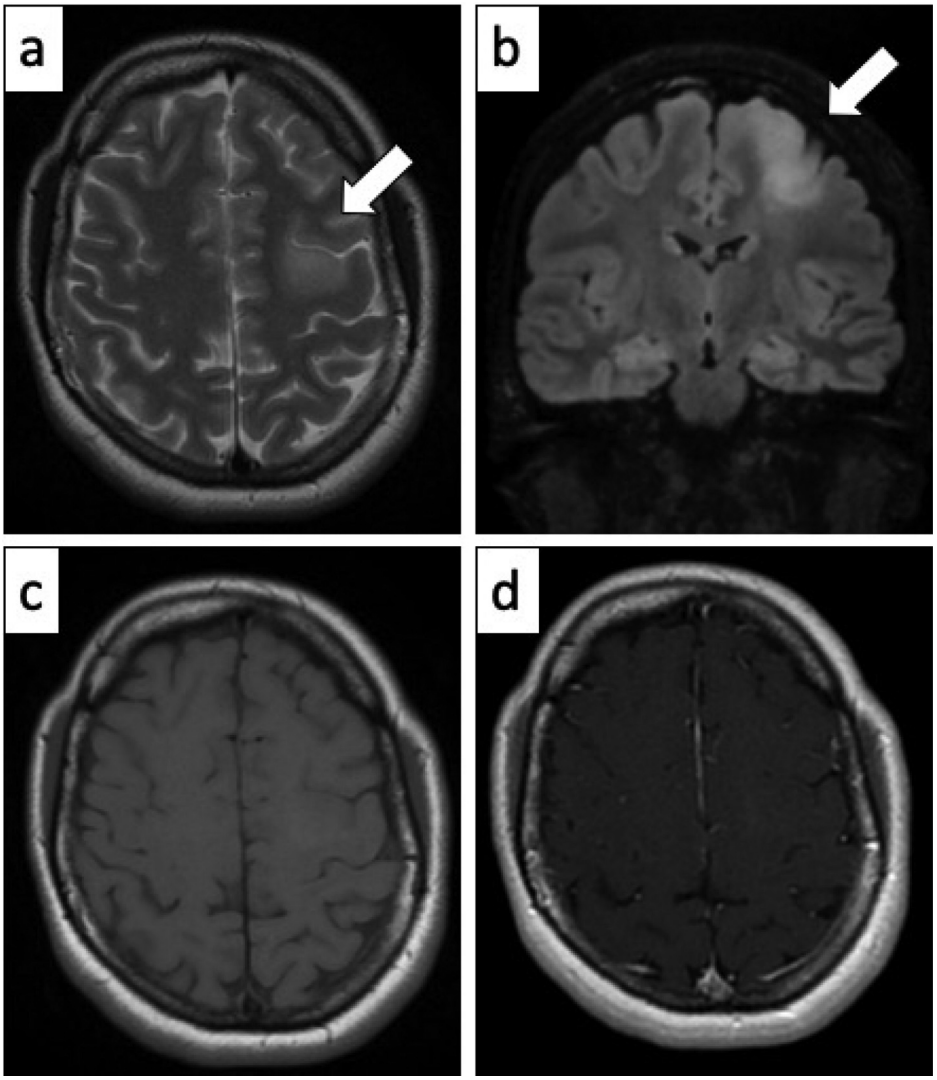

Figure 1 (a) Axial T2-weighted magnetic resonance (MR) image shows a slightly hyperintense mass located in the superior left frontal gyrus (arrow), mainly located at the level of white matter with extension into the adjacent cortex. On Coronal Fluid Attenuated Inversion Recovery (FLAIR) image (b) it appears hyperintense compared to the normal white matter without showing any sign of edema or mass effect on adjacent structures. On T1-weighted MR image (c) appears isointense to the normal brain, not visible at all. After intravenous injection of gadolinium based contrast media (d), it shows no enhancement.

gastrointestinal and respiratory origin; however, hematologic malignancies have been reported in a number of cases [5—10].

Atas et al. described a RP in a child with medulloblastoma as a late side effect of cisplatin-based chemotherapy [6]. However, to the best of our knowledge, no case reports covering RP associated with untreated brain tumors have been reported to date.

Hsu et al. were the first ones to hypothesize that the association between digital ischemia, with or without RP, and malignancies represent a specific clinical syndrome [5]. Subsequently, this hypothesis was confirmed and the term paraneoplastic acral vascular syndrome (PAVS) was coined.

PAVS affects the hands in 94% of patients and the feet in only 30%, always involving digits. Acute digital necrosis is the clinical onset in 40% of the cases, RP in 71% and acrocyanosis only in 24%. In the case series reported by Poszepezynska et al. [11], the mean age of patients was 55.1 years, the male-female ratio was 0.89 and 67% of patients were smokers. In this case series, there was a prevalence of hematologic malignancies.

Therefore, PAVS typically affects middle-aged patients, without a prevalence of gender, and sometimes has an acute onset and a rapidly progressive clinical course, often characterized by ulcers and necrosis resistant to medical treatment.

In our case, the early diagnosis of cancer avoided the clinical manifestations associated with the advanced stages of the disease.

Regarding the temporal relationship between vascular manifestations and malignancy, PAVS can be classified in three main types: in type 1, the vascular manifestations precede the diagnosis of malignancy by weeks or months, but the malignancy is untreatable and the patient dies while

suffering from digital ischemia. In type 2, the vascular manifestations precede the diagnosis of malignancy, this one is successfully treated and digital ischemia resolves spontaneously after treatment of the underlying malignancy. In type 3, the patient had a previous malignancy without PAVS, successfully treated for a short or long period, but at one point he develops vascular manifestations indicating a cancer recurrence [11].

Our young patient had type 2 PAVS because the RP preceded the diagnosis of astrocytoma and the surgical resection of malignancy resulted in a complete disappearance of the vascular manifestations, which no longer recurred in a 5 years follow-up.

Regarding the pathogenesis, the main hypotheses proposed for PAVS include [11,12]:

- ischemia from tumor antigen immune complex deposition in the small vessels of the digits;
- invasion of the endothelium by neoplastic cells;
- vasculitis induced by antibodies against tumor antigens;
- altered neuro-mediated vasomotor regulation secondary to infiltration of the regional nervous plexus by the tumor;
- paraneoplastic cryoglobulinemia;
- secretion of vasoconstrictor substances by the tumor;
- hypercoagulability;
- hyperviscosity;
- increased platelet aggregation.

In a histological study, leukocytoclastic vasculitis associated with intimal proliferation has been described [13].

Given the rarity of the disease, no randomized clinical trials investigating the treatment modalities have been performed. Treatment options currently include corticosteroids, heparin, nifedipine, prostanoids and plasmapheresis, but the only treatment that has been considered effective is the radical resection or chemotherapy-induced remission of the underlying malignancy [11,12]. In the case series by Poszepezynska et al. [11], there were no recurrences of PAVS after treatment of the tumor.

Even in our case, once the radical resection of the astrocytoma was performed, complete resolution of the RP was obtained and there was no need to start any long-term pharmacological therapy.

Conclusion

Our case showed some interesting features. Firstly, RP was secondary to an untreated brain tumor and, to the best of our knowledge, this is the first case of PAVS associated to an untreated brain tumor reported in the medical literature. Secondly, the age of our patient was lower compared to the mean age of patients with PAVS reported in case series. Thirdly, both vascular and tumor clinical manifestations developed simultaneously and were rather mild. This findings led us to recommend that secondary RP associated with malignancy should be suspected not only in patients with severe vascular manifestations refractory to treatment, but also in those with mild vascular manifestations. It should be emphasized that especially in these cases, accurate and detailed medical history and physical examination play a key role in leading physicians to rule out an underlying malignancy, which represents a rare but potentially fatal cause of secondary RP.

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Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Belch J, Carlizza A, Carpentier PH, Constans J, Khan F, Wautrecht JC, et al. ESVM guidelines — the diagnosis and management of Raynaud's phenomenon. VASA 2017;46:413—23.
[2] Pistorius M-A, Carpentier P-H, Le groupe de travail « Microcirculation » de la Société française de médecine vasculaire. Minimal work-up for Raynaud syndrome: a consensus report. Microcirculation Working Group of the French Vascular Medicine Society. J Mal Vasc 2012;37:207—12.
[3] Attal R, Lazareth I, Angelopoulos G, Priollet P. Ranibizumab and digital ischemia. J Med Vasc 2018;43:65—9.
[4] Hamilton WF. Carcinoma of the oesophagus and Raynaud's disease. Can Med Assoc J 1920;10:670—1.
[5] Hsu ST, Lee YY, Lie MF. Symmetrical peripheral gangrene of sudden onset — a paraneoplastic syndrome?— a case report and review of the literature. Dematol Sinica 1996;14:82—8.
[6] Atas E, Korkmazer N, Artik HA, Babacan O, Kesik V. Raynaud's phenomenon in a child with medulloblastoma as a late effect of chemotherapy. J Cancer Res Ther 2015;11:666.
[7] Villano F, Peixoto A, Riva E, Di Matteo C, Díaz L. Digital ischemia as an unusual manifestation of Hodgkin's lymphoma. Case Rep Hematol 2018;2018:1980749.
[8] Allen D, Robinson D, Mittoo S. Paraneoplastic Raynaud's phenomenon in a breast cancer survivor. Rheumatol Int 2010;30:789—92.
[9] Warrier V, Ahmad A, Alshatti Y, Jafar A. Digital necrosis with squamous cell carcinoma of the tonsil. Int Med Case Rep J 2016;9:159—62.
[10] Khammar Z, Ouazzani M, Bennani B, Oubelkacem N, Berrady R. Digital ischemia revealing multiple myeloma. J Med Vasc 2018;43:61—4.
[11] Poszepczynska-Guigné E, Viguier M, Chosidow O, Orcel B, Emmerich J, Dubertret L. Paraneoplastic acral vascular syndrome: epidemiologic features, clinical manifestations, and disease sequelae. J Am Acad Dermatol 2002;47:47—52.
[12] Kopolovich DM, Lagonosky DD, Greco AA, Weaver E, Malhotra R, Holmes P, et al. Paraneoplastic acral vascular syndrome. Med Forum 2013:14 [Article 14].
[13] Friedman SA, Bienenstock H, Richter IH. Malignancy and arteriopathy. A report of two cases. Angiology 1969;20:136—43.

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