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D. Velásquez*, P. Zamberk, R. Suárez, P. Lázaro

Department of Dermatology, University General Hospital Gregorio Marañón, Madrid, Spain

*Corresponding author.
E-mail address: diana_velazquezt@yahoo.es (D. Velásquez).

Fulminant digital necrosis in a patient with prostate adenocarcinoma

To the Editor:

Association between thrombotic disorders and malignancy is rare but has been well described[1]. Digital ischaemia and neoplasia were first reported in 1884 by O'Connor.[2] After that very few case reports of digital ischaemia and neoplasia have been published. Most of the reports showed digital, bilateral and symmetric ischaemic lesions involving mainly upper extremities beginning as cyanosis or digital colour changes with cold exposure (Raynaud syndrome) and rapidly progressing to gangrene. Arteritis, hypercoagulability and hyperviscosity are postulated as mechanisms responsible for digital vasospasm and arterial obstruction in association with neoplasia.

Digital necrosis as paraneoplastic syndrome was reported in association with several neoplasias including haematological and solid tumours but not with prostate adenocarcinoma.[3]

A 73-year-old Chinese male was admitted to the hospital because of bilateral, symmetric digital ischaemia evolving to gangrene in two months (Figure 1A, B). The patient had no previous history of Raynaud, livedo, autoimmune disease, drug or toxic exposure, past or present infections, or neoplasia. He denied the use of medicinal herbs. An arteriovenous ecodoppler showed no alterations.

His blood and serum test showed severe eosinophilia (absolute count 6000/mm^3), augmented Eritrosedimentation rate and PCR, positive Rheumatoid Factor (RF), and polyclonal hypergammaglobulinaemia, HIV, HBV and HCV were negative. Bone Marrow aspiration showed no abnormal findings. Biopsy of perilesional skin showed leucocytoclasic vasculitis, fibrinoid thrombi and focal epidermic necrosis. Immunologic tests for ANA, cryoglobulins, C ANCA, P ANCA, anti-MPO, anti-PR3, lupus anticoagulant, Ig G, IgM Acls and B2 GPI were negative.

He added low extremities pain and paraesthesia with electromyographic signs of peripheral axonal neuropathy. There were no other signs or symptoms of systemic vasculitis.

Due to the rapid progression of digital lesions treatment with glucocorticoids and ciclofosfamide was started. Digital lesions became stable (Figure 2A,B) with normalisation of eosinophil counts, gammaglobulin values and negativisation of RF. Clinical examination revealed a prostatic nodule coincident with an increased PSA value. A prostate biopsy was proposed but patient refused the procedure. After discharge he continued well receiving ciclofosfamide for 20 months until he developed acute urinary obstruction and eosinophilia (absolute count 800/mm^3). A rectal examination showed prostate tumour and the PSA was 94.77 g/ml. A transrectal biopsy was done and diagnosis of adenocarcinoma (Gleason 5+4) was made. Immunosupression was discontinued and he started complete androgenic blockade with resolution of obstructive urinary symptoms and normalisation of PSA value, sustaining digital lesions improvement.

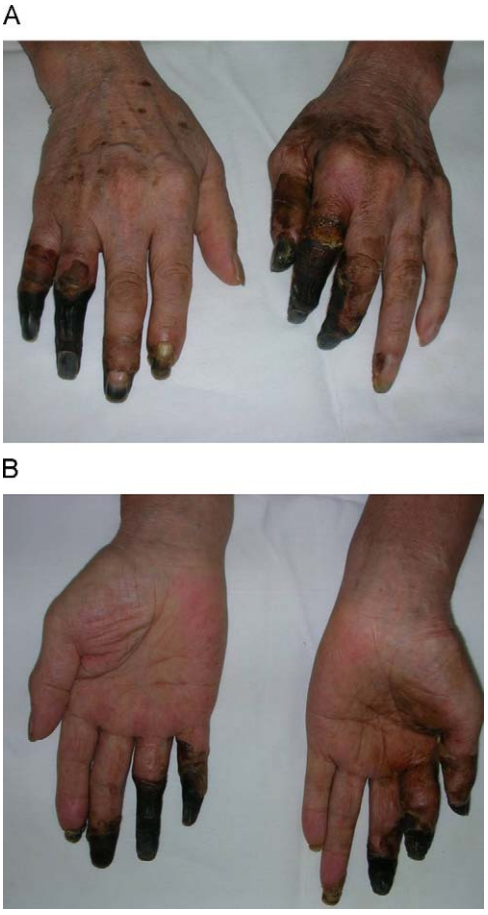

Figure 1 (A,B). Pre-treatment. An area of necrotic skin on the left palm and several necrotic fingers in both hands can be observed.

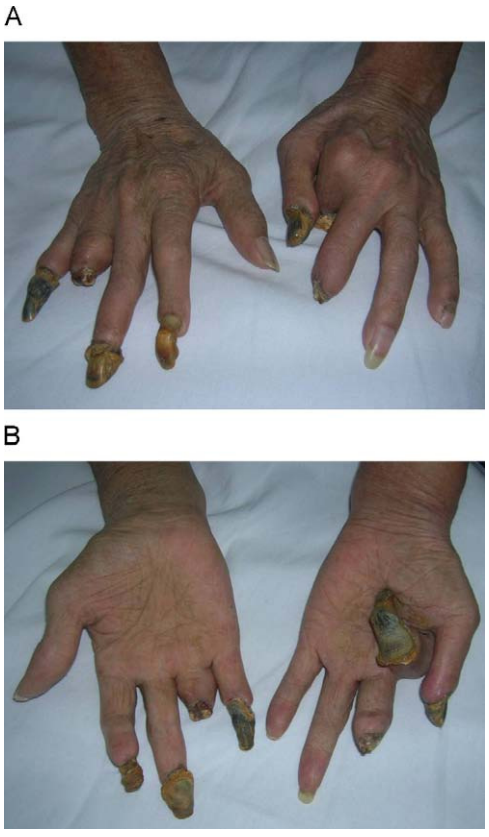

Figure 2 (A,B). Post treatment, after 20 months. Spontaneous healing of necrotic lesions is in progress.

Digital ischaemia, although uncommon, has been described as a paraneoplastic syndrome in different kinds of neoplasias. The probable mechanisms of digital arterial obstruction in association with malignancy are arteritis, hypercoagulability and hyperviscosity.

Arteritis of diverse aetiologies has been clearly associated with digital artery vasospasm and obstruction producing finger ischaemia and gangrene.[4–6] Arteritis in the affected vessels has been reported in some patients with tumour associated digital ischaemia. The cause of the arteritis is unknown but it is suggested that tumour antigen-antibody complexes deposition and subsequent complement activation in contact with the arterial wall induce this digital vasculitis, which improves with reduction of the tumour burden by therapy.[7]

Viscosity abnormalities have also been proposed as a mechanism of ischaemia, which could be attributed to a severely elevated whole blood viscosity or an increase in circulating blood proteins (for example: cryoglobulins).[7] Moreover hyperviscosity caused by cryoglobulinaemia and arteritis may coexist.

Hypercoagulability in the absence of arteritis or hyperviscosity has been detected in 50–90% of patients with malignant tumours, especially those with metastases.[8,9]

Digital necrosis has been described in several opportunities as a paraneoplastic syndrome in different set of tumours but has not been reported as initial presentation in prostate cancer. Moreover there are few cases of vasculitic digital necrosis proved by biopsy in gangrene secondary to neoplasia,[3] as we report here. The detection of antibodies in patient serum against tumour antigens by immunofluorescence would be very useful to prove this association but when the patient acceded to the biopsy he was under immunosuppression and his digital lesions were no more active, thus performing this test lost value. Other probable causes of vasculitic digital necrosis were excluded such as septic vasculitis since the patient did not show signs of infection, or hypersensitivity vasculitis since there was no history of offending drug consumption before development of lesions. There were no other signs of major organ involvement which discarded Systemic Vasculitic Syndromes.

The relationship with hypereosinophilia is another consideration in our patient. In this case digital necrosis could also be explained by the hypereosinophilic syndrome (HES) associated to neoplasia. Patients with HES may experience cold-induced Raynaud's phenomenon and can develop finger or toe digital necrosis. Reported cases have occurred in those with HES alone and in a patient with eosinophilia and acquired immunodeficiency syndrome who had digital vasculitis arteriographic evidence.[10]

In our case the severity and rapid progression of lesions observed could be attributable to the association of at least two mechanisms: the arteritis and hypereosinophilia.

Digital necrosis associated with malignancy is severe and rapidly progressive within a few days. In this case, immunosupression resulted in a rapid symptomatic relief of pain with stabilisation of distal digital necrosis. Long-term sustained remission was achieved by tumour treatment with hormonal blockade.

Excluding other causes of vasculitis, the presence of severe vasculitic lesions confined to both hands simultaneously with prostatic adenocarcinoma could suggest a causal relationship.

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M.V. Paolini[a,*], G. Jankilevich[b], C. Graziano[c], D.S. Fernández Romero[a]

[a]*Immunology Unit Hospital Carlos G. Durand. Buenos Aires Argentina, Argentina*
[b]*Oncology Section Hospital Carlos G. Durand. Buenos Aires Argentina, Argentina*
[c]*Urology Division. Hospital Carlos G. Durand. Buenos Aires Argentina, Argentina*

*Corresponding author.
E-mail address: virpaolini@gmail.com (M.V. Paolini).

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Food allergy to pumpkin seed

To the Editor:

Pumpkin (*Cucurbita maxima*) belongs to the Cucurbitaceae family. Its seeds contain large quantities of proteins (35%) and unsaturated fatty acids (50%, mainly linoleic acid and oleic acid), tocopherols, and phytosterols. The seeds are usually consumed toasted as an appetiser, in salads, or as an additive to bread. The flour obtained by grinding the seeds is mixed with water and used as bait by fishermen.[1] Unlike the other members of the Cucurbitaceae family,[2] pumpkin seed is not a common cause of food allergy, and there have been few reports of allergic reactions after ingestion.[1]

We report the case of a 33-year-old man referred to our clinic who, on several occasions, had presented facial oedema and erythema accompanied by a sensation of dyspnoea 15 min after eating toasted pumpkin seeds (*Cucurbita maxima* species). Each episode required emergency medical care with antihistamines and corticosteroids. He tolerated pumpkin, melon, watermelon, and nuts (peanut, hazelnut, almond, sunflower seed, and walnut) with no problems. He also reported facial oedema and erythema after eating peach, apple, unpeeled pear, and orange. He tolerated squeezed juices of these same fruits peeled. He tolerated other fruits and vegetables without problems. He also had a 3-year history of pollen-induced rhinoconjunctivitis, and had taken oral antihistamines on demand. He had never received pollen-specific immunotherapy.

He underwent skin prick testing with the most common commercial pollen extracts in our practice area, namely, profilin, lipid transfer protein (LTP) of peach (30 μg/mL) (ALK-Abelló, Madrid, Spain), fruit, and nuts (Leti, Barcelona, Spain). The patient presented positive results for grasses, olive, cypress, plantain, *Chenopodium*, pumpkin seed, almond, hazelnut, and LTP of peach, melon, and apple. The result of prick-prick testing with pumpkin seed was positive (wheal size, 22 × 20 mm). Prick-prick testing with the two main pumpkin species of the Mediterranean area (*Cucurbita pepo l.* and *Cucurbita maxima duchesne*) were positive.

Total IgE was 1272 kU_A/L. Specific IgE was determined (CAP System, Phadia, Uppsala, Sweden) against grasses (>100 kU_A/L), olive (9.09 kU_A/L), and the recombinant allergens of timothy (*Phleum pratense*): rPhl p 1(72.30 kU_A/L), rPhl p 5 (72.30 kU_A/L), rPhl p 7 (polcalcin), and rPhl p 12 (profilin of *Phleum pratense*) (<0.35 kU_A/L).

The results of determination of specific Ig (ADVIA-Centaur) against apple profilin (Mal d 4), 2S albumin (Sin a 1, the major mustard allergen), vicilin (Len c 1, the major lentil allergen), and chitinases (Prs a 1, a class 1 chitinase of avocado and Cas s 5, a class 1 chitinase of chestnut) were negative. Specific IgE against peach LTP, Pru p 3, was 0.65 kU_A/L.

To confirm the diagnosis, we suggested the patient to carry out a controlled specific challenge test with pumpkin seeds, but he declined the proposal.

In order to study the pumpkin seed allergens recognised by our patient, we first obtained pumpkin seed extract at 10% (w/v) in sodium chloride 1.8%, for 90 min at 4 °C with magnetic shaking. After centrifugation, the supernatant was filtered through 0.2 μm pore size microfilter and kept at −20 °C until used.

Both the extract and the molecular weight markers were analysed using SDS-PAGE (acrylamide content, 16%) under non-reducing conditions, according to the method described by Laemmli.[3] The polyacrylamide gel proteins were electrophoretically transferred to nitrocellulose paper strips,[4] which were then saturated with 5% bovine serum albumin (BSA) in phosphate-buffered saline (PBS) for 1 h at room temperature and incubated for 18 hs with the patient's serum diluted 1:5. A nitrocellulose strip containing milk thistle extract incubated with 5% BSA in PBS was used as a negative control. The strips were washed in 0.1% Tween-20 in PBS and incubated for 2 h at room temperature with human anti-IgE monoclonal antibody (HE-2) obtained from ascites and diluted 1:3000.[5] The strips were washed again and incubated a third time at room temperature with peroxidase-marked rabbit anti-mouse IgG (RAM-HRP, Calbiochem) diluted 1:5000. Finally, the strips were washed and proteins capable of fixing IgE were detected using chemoluminescence (ECL, Amersham Bioscience) according to the manufacturer's instructions.

Figure 1 shows the results of immunodetection. The patient's serum IgE recognised proteins of different molecular weights in the extract. The most intense band corresponded to a protein weighing approximately 12 kDa.

In order to determine whether the 12-kDa band corresponded to an LTP present in the extract, immunodetection was performed with a specific polyclonal antibody of Pru p 3. However, the polyclonal antibody was unable to recognise any bands in the extract; therefore, it was not possible to demonstrate the existence of an LTP that was homologous to Pru p 3.

Pumpkin seed allergy is rare. Previous studies on allergy to this[2] and other members of the Cucurbitaceae family[6] have pointed to profilin as one of the major allergens. However, although the patient we report had rhinoconjunctivitis caused by grass pollen, he presented neither profilin-specific antibodies, nor antibodies against other food allergens such as 2S albumins, vicilins, or chitinases. He