sciendo
Internal Medicine 2019 vol. XVI No. 3 - www.srmi.ro
10.2478/inmed-2019-0069

SYSTEMIC SCLERODERMA OR PARANEOPLASTIC SYNDROME?

Cristina Vrâncianu[1,2], Carmen Sandu[1], Laura Georgescu[1], Diana Dinescu[1], Ioan Ancuța[1,2], Mihai Bojincă[1,2], Ana Maria Gheorghiu[1,2]
[1]"Dr. Ioan Cantacuzino" Clinical Hospital
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest
Corresponding author:
Ana Maria Gheorghiu, MD
Internal Medicine and Rheumatology Department, Cantacuzino Hospital
Ion Movila 5-7, 020475 Bucharest, Romania
tel +40 21 210 7113; fax +40 21 210 3410
e-mail: ana.gherghe@gmail.com

Rezumat

Introducere. *Bolile reumatice inflamatorii reprezintă uneori prime manifestări ale unei neoplazii.*

Prezentarea cazului. *Pacientă în vârstă de 57 de ani, mare fumătoare, se internează în urgență pentru necroza pulpei degetului 3 de la mâna dreaptă, apărută de 2 zile, cu debut al ischemiei cu o săptămână anterior internării. Mai acuză fenomen Raynaud, xerostomie și disfagie la solide, precum și dispnee la eforturi medii, cu debut de 6 luni, pentru care a fost evaluată pneumologic și prin tomografie computerizată toracică, care a decelat o masă ganglionară mediastinală evolutivă dimensional, neinvestigată suplimentar.*

Clinic prezintă facies de icoana bizantină, sclerodactilie și microstomie ușoară, și zonă de necroză uscată de 1.5/1 cm în pulpa degetului 3 de la mâna dreaptă, în rest fără modificări remarcabile. Analizele de laborator evidențiază anticorpi antinucleari cu anti SS-A pozitivi, precum și sindrom inflamator seric important. Consultul chirurgical exclude trombangeită obliterantă sau altă patologie de vase mari.

Diagnosticul prezumptiv este colagenoză nediferențiată cu elemente de sclerodermie sistemică și sindrom Sjögren, cel mai probabil secundară unei formațiuni tumorale mediastinale. Biopsia mediastinală obiectivează prezența unei metastaze mediastinale heterogene de origine necunoscută, iar investigațiile efectuate: imunohistochimie, testări multiple ale unor mutații genetice, tomografie computerizată toraco-abdomino-pelvină, mamografie, examen Papanicolau și tomografie cu emisie de pozitroni nu identifică sursa de pornire, întârziindu-se astfel inițierea tratamentului oncologic.

Internal Medicine

Clinical cases

Concluzie. *Este vorba de un caz rar de colagenoză nediferențiată cu elemente de sclerodermie sistemică și de sindrom Sjögren, cel mai probabil paraneoplazică, cu metastaze mediastinale, dar tumoră primară nedeterminată. Subliniem importanța diagnosticului precoce la acești pacienți pentru evitarea apariției complicațiilor și îmbunătățirea prognosticului.*
Cuvinte cheie: *colagenoză, necroză digitală, manifestare paraneoplazică, cancer cu tumoră primară nedeterminată, metastaze mediastinale.*

Abstract

Introduction. *Inflammatory rheumatic diseases are sometimes the first manifestation of neoplasia.*

Case presentation. *A 57 year old female patient, heavy smoker, is admitted to our clinic for 2 days old pulp necrosis of the third finger, right hand, with onset of ischemia 1 week before admission. Other manifestations were Raynaud's phenomenon, dry mouth, dysphagia and shortness of breath after moderate physical activity with a duration of about 6 months. She was repeatedly followed-up by a pulmonologist with chest computer tomography, which detected a dimensional evolutionary mediastinal lymph node, but not investigated further. The patient had skin thickening of the hands and face, microstomia and an area of dry necrosis of 1.5/1cm in the pulp of the third finger, right hand. Laboratory tests show the presence of antinuclear antibodies with positive anti SS-A antibodies and elevated levels of serum inflammatory markers. Vascular surgery examination excludes thromboangiitis obliterans or other large vessel diseases. The presumptive diagnosis is undifferentiated connective tissue disease with systemic sclerosis and Sjögren syndrome elements, most likely secondary to the mediastinal tumor. Mediastinal biopsy shows a heterogeneous metastasis of unknown origin, and further investigations: immunohistochemistry, multiple gene mutations tests, computed tomography scan of the chest, abdomen, and pelvis, mammography, Papanicolaou test and positron emission tomography scan did not identify the primary tumor, thus delaying oncologic treatment.*

Conclusion. *Case of undifferentiated connective tissue disease with elements of systemic sclerosis and Sjögren syndrome, most probably paraneoplastic, with chest metastasis of unknown origin, in which diagnosis and treatment were delayed due to lack of primary tumor identification.*

Keywords. *Connective tissue disease, digital necrosis, paraneoplastic syndrome, cancer of unknown primary site, mediastinal metastasis.*

Introduction

Paraneoplastic syndromes are malignancy symptoms, which are directly linked to the primary tumor or its metastases[1]. Approximately 8-10% of cancer patients suffer from a paraneoplastic syndrome[1]. In some cases, the paraneoplastic syndrome precedes the neoplasia.

Their recognition is therefore important as it can lead to the early diagnosis of a neoplasia in a stage with high chances of treatment success. Inflammatory rheumatic diseases sometimes represent the first manifestations of a neoplasia. Among the most frequent we mention dermatomyositis, hypertrophic osteoarthropathy or leukocytoclastic vasculitis[1]. Although the association between systemic scleroderma (SSc) and neoplasia is well known, it is however not regarded as high risk[2].

Case presentation

Female patient aged 58, heavy smoker (30 pack-years), known with history of arterial hypertension, tumorectomy of left breast for benign nodule, plastic surgical intervention with bilateral breast implant (1994) and depressive disorder in remission, was admitted to our Clinic via the emergency department, in March 2018, for the pulp necrosis of the 3rd finger of the right hand, with onset two days ago, but with onset of ischemia one week prior to admission. She also accuses Raynaud phenomena, with onset in the spring of year 2017, xerostomia and solid dysphagia.

Complete anamnesis reveals additionally dyspnea on exertion of moderate level and nocturnal sweats for about 6 months, for which she has been assessed by a pulmonologist via chest CT scan in October 2017 and February 2018, during which the presence of a dimensional evolutive nodular mass has been revealed, but which has been submitted to no further investigations.

Clinical examination

On admission, the patient was afebrile, had a facies which suggested a ”byzantine icon” - type, with mild microstomia, long, thin nose and perioral wrinkles, sclerodactilia, diffuse cutaneous hyperpigmentation, with an area of dry necrosis of 1.5/1 cm in the pulp of the 3rd finger of the right hand (Figure 1, Figure 2), scars at the level of 2nd and 3rd fingers of the left hand post reconstruction surgery following childhood trauma; she was also cardio-pulmonary stable, with no other significant elements at the clinical examination.

Investigations

Usual laboratory tests, including complete blood count(CBC) and biochemistry panel (creatinine, uric acid, transaminases, glycemia) were within normal limits, but with a moderate serologic inflammatory syndrome with C-reactive protein (CRP) of 43.00 mg/L (N<5mg/L) and erythrocyte sedimentation rate (ESR) of 41 mm/h (N<30mm/h). From an immunological point of view, antinuclear antibodies have been intensely positive, with anti-SS-A(Ro) positive. Antibodies c-ANCA and p-ANCA have been negative, and so has been the antiphospholipid antibody profile. Abdominal ultrasonography and nailfold capillaroscopy have been conducted, both within normal limits.

An examination of vascular surgery has been conducted with arterial and venous Doppler ultrasonography at the level of upper limbs, at which no large vessel stenoses were observed, but however indirect signs of microvasculopathy have been detected.

Internal Medicine

Clinical cases

The presumptive diagnosis was undifferentiated collagenosis with elements of systemic scleroderma and Sjögren syndrome, most probable secondary to a mediastinal tumor mass. At discharge a biopsy of the lymphonodular mass was recommended.

During hospitalisation, the patient has been treated with vasodilator therapy Alprostadil 20 micrograms, 2 vials/day iv. and Sulodexid 250 ULS, 2 tablets/day, anticoagulant therapy Fraxiparine of 0.6 mL, 2 vials, 2 times per day, and antalgic therapy (Tramadol 100mg/2mL) 2 vials/ day, well tolerated, with cessation of necrosis evolution and its self-limitation at the necrotic area from the moment of hospital admission.

In April 2018, a mediastinal biopsy has been performed at the "Marius Nasta" Institute, which was complicated with secondary right pneumothorax, associated with cervicothoracic subcutaneous and mediastinal emphysema, and resuscitated cardiac arrest. Right minimal pleurotomy has been conducted with insertion of a thoracic drainage tube, with remission of symptoms. The histopathological and immunohistochemical analysis of the biopsy fragment collected from the mediastinal mass sustain the diagnosis of lymphonodular metastasis with unknown origin. The hypotheses of the tumor origin have been genital and pulmonary; however none of them have been confirmed at the repeated immunohistochemical and histopathological analyses.

In evolution, in May 2018, the patient underwent the amputation of the distal phalanx and half of the medium phalanx of the 3rd finger from the right hand, and in June 2018 she was readmitted in our clinic for the pulp necrosis of the second finger from the left hand, developed with approximately 3 weeks prior admission (Figure 3), unintentional weight loss of approximately 12 kg in the past few months, and in order to continue the investigations. A gynecological exam was performed, including Papanicolaou exam and mammography, all within normal limits. Moreover, the native and contrast-enhanced CT scan of the chest, abdomen and pelvis was repeated; however the primary tumor could not be identified. In these conditions, PET-CT scan was recommended. Moreover, during hospitalisation, the patient was treated with vasodilator therapy Alprostadil in iv infusion, 14 days, antibiotherapy with ciprofloxacin and ceftriaxone, replaced afterwards with oxacillin (according to the antibiogram) and antalgic treatment, with self-limitation of the necrosis area at the moment of discharge. After discharge, the evolution of the necrosis was unfavorable, with the amputation of the distal and medial phalanges of the second finger of the left hand (Figure 4).

In August 2018, the PET-CT scan revealed a metabolically active lymphonodular mass,

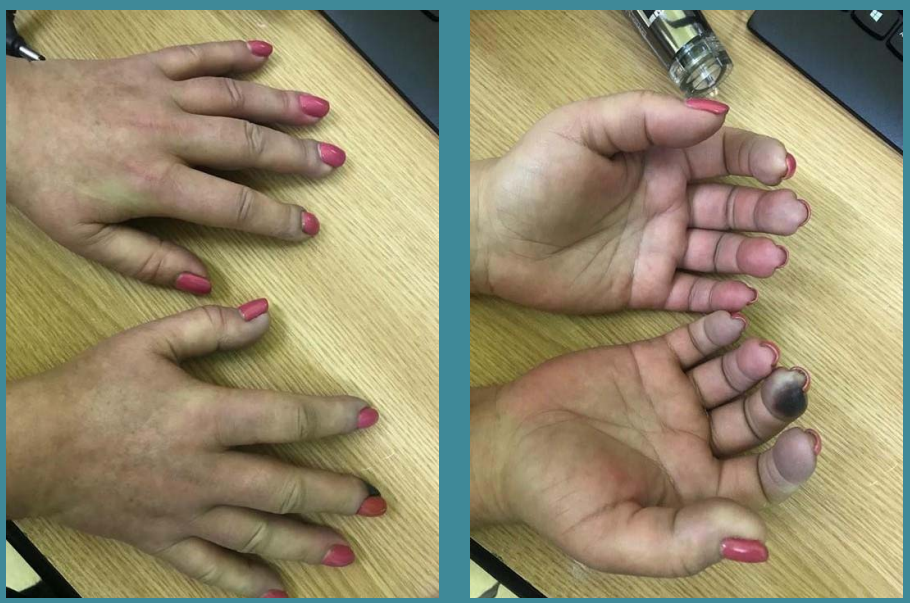

Figure 1. *Aspect of hands at first presentation (sclerodactilia, diffuse skin hyperpigmentation, dry necrosis of 1.5/1 cm in the pulp of the third finger of the right hand)*

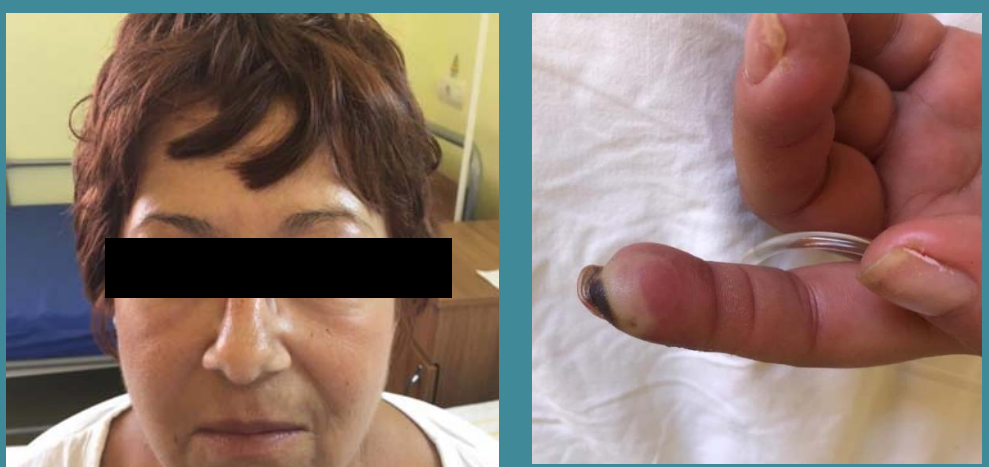

Figure 2. *Facies which suggests a "byzantine icon" - type (mild microstomia, long, thin nose and perioral wrinkles)*

Figure 3. *The aspect of the finger necrosis at the second hospitalization*

Figure 4. *The aspect of hands in the present*

situated superiorly and inferiorly paratracheally. Other metabolically active adenopathies were situated right supraclavicular, prevascular, infracarinal and right pulmonary hilar. The PET-CT scan did not reveal any primary tumor cause. In addition, an MRI of the brain has been conducted without secondary cerebral tumors, and a breast MRI, without clear suggestion for neoplasia.

In September 2018, it was proposed within a multidisciplinary oncologic commission (Elias Oncology) the re-performing of the biopsy of the mediastinal mass. The conclusion of the second biopsy is the diagnosis of non-small-cell lung adenocarcinoma. The presence of the mutation EGFR has been tested, the ALK rearrangement, as well as the PDL-1 expression, but all of them have rendered negative results at repeated testing. Therefore, the patient is not eligible for targeted therapy or immunotherapy. Only in March 2019, after performing a pre-treatment summary, polychemotherapy has been initiated with pemetrexed and cisplatin for the pulmonary neoplasia (without identification of the primary pulmonary tumor), with mediastinal metastases, well tolerated, which the patient undergoes until the present moment (the moment of article submission).

Discussions

We have presented the case of a female patient with paraneoplastic undifferentiated collagenosis with elements of systemic scleroderma and Sjögren syndrome, with primary site of tumor undetermined. The presence of metastases in the absence of the primary tumor, known in literature as cancer of unknown primary site (CUP), features an etiology and pathogenesis insufficiently known, but in general it is considered that metastases get an advantage of growth compared to the primary tumor. It represents approximately 3-5% of all malignant tumors, being more frequent among male patients. The majority of patients have a poor prognosis, with a life expectancy under 12 months[3]. In comparison with literature data, the singularity of the case presented was that the patient was female, with a life expectancy exceeding 12 months.

The post-mortem studies have identified the primary tumor especially at the level of the lungs and pancreas, and the histological forms the most frequently found have been adenocarcinoma (50-70%) and undifferentiated carcinoma (20-30%)[3]. Most probably the female patient presented has suffered from non-small-cell lung adenocarcinoma.

Concerning the association of systemic scleroderma with paraneoplastic disorders, it can coexist with a cancer[4], but this association is probably underestimated due to the high mortality rate given by systemic scleroderma. Disease manifestations such as pulmonary arterial hypertension, pulmonary fibrosis or sclerodermal renal crisis make systemic scleroderma the type of collagenosis with the highest mortality rate[5].

The features that point to a paraneoplastic systemic scleroderma are the onset of symptoms at patients of advanced age (aged over 50 years), with acute onset of the Raynaud phenomenon with a rapid evolution to necrosis and weak response to vasodilator therapy, the presence of sclerodactilia, significant alteration of the general health (asthenia, weight loss), the presence of progressive cutaneous fibrosis which extends to the neck and body trunk, as well as the history of exposure to carcinogenic factors[6,7]. Also, it seems that positive anti-topoisomerase I antibodies are associated with the presence of paraneoplastic syndromes[4]. Among all these criteria, our patient encompasses at least four enumerated features, which makes the suspicion of systemic scleroderma as paraneoplastic syndrome to be well justified in this case.

The antinuclear antibodies (ANA) that are most often encountered in rheumatic diseases represent a lower frequency in the malignant disorders, but still with an important percentage of about 10-20%[8,9]. There are studies that have evaluated the prevalence of ANA in patients with malignant diseases and the possibility that their presence could be involved in the onset of paraneoplastic syndromes and the development od musculoskeletal symptoms. It seems there is a high incidence of ANA in malignant disorders and in the case of neoplastic patients with positive ANA, the frequency of paraneoplastic syndromes and musculoskeletal symptoms is much more higher compared to neoplastic patients with negative ANA or with healthy subjects[10]. A study conducted in 2018 has confirmed these results , ANA having a frequency of almost 40% among the patients with paraneoplastic syndromes included in the study[11].

Even in the case presented there is a high index of suspicion of paraneoplastic

collagenosis, we mention that in the present there is no accurate method to differentiate between a paraneoplastic syndrome and the primary affection. The continuation of polychemotherapy with the follow-up of the evolution of collagenosis and at the same time of the lymphonodular metastases could offer in time an answer, but for the moment the prognosis remains negative. The treatment of the neoplasia is the most important, however the rapidly progressive and severe peripheral vascular impairment, with dry necroses of the fingers which lead to amputations, require also the continuation of vasodilator treatment.

In **conclusion**, we have presented the case of a female patient with undifferentiated collagenosis with elements of systemic scleroderma and Sjögren syndrome, most probable paraneoplastic, with mediastinal lymphonodular metastases, in which case the diagnosis and treatment have been delayed because of lack of localisation of the primary site of tumor.

Data published with the informed consent the patient

References:

1. Pelosof MD, PHD LC, Gerber MD DE. Paraneoplastic Syndromes: An Approach to Diagnosis and Treatment. Mayo Clin Proc. 2010;

2. Zeineddine N, Khoury L El, Mosak J. Systemic Sclerosis and Malignancy: A Review of Current Data. J Clin Med Res. 2016;

3. Krämer A. Metastases in the Absence of a Primary Tumor – Advances in the Diagnosis and Treatment of CUP Syndrome: In reply. Dtsch Aerzteblatt Online. 2009;

4. Szekanecz Z, Szekanecz É, Bakó G, Shoenfeld Y. Malignancies in autoimmune rheumatic diseases - A mini-review. Gerontology. 2010.

5. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: A systematic review and meta-analysis of cohort studies. Rheumatol (United Kingdom). 2012;

6. Racanelli V, Prete M, Minoia C, Favoino E, Perosa F. Rheumatic disorders as paraneoplastic syndromes. Autoimmunity Reviews. 2008.

7. Ciołkiewicz M, Domysławska I, Ciołkiewicz A, Klimiuk PA, Kuryliszyn-Moskal A. Coexistence of systemic sclerosis, scleroderma-like syndromes and neoplastic diseases. Polskie Archiwum Medycyny Wewnetrznej. 2008.

8. Madrid FF, Maroun MC. Serologic laboratory findings in malignancy. Rheumatic Disease Clinics of North America. 2011.

9. Zuber M. Positive antinuclear antibodies in malignancies [3]. Annals of the Rheumatic Diseases. 1992.

10. Solans-Laqué R, Pérez-Bocanegra C, Salud-Salvia A, Fonollosa-Plá V, Rodrigo MJ, et al. Clinical significance of antinuclear antibodies in malignant diseases: Association with rheumatic and connective tissue paraneoplastic syndromes. Lupus. 2004;

11. Wen J, Ouyang H, Yang R, Bo L, Zhang Y, Tang M, et al. Malignancy dominated with rheumatic manifestations: A retrospective single-center analysis. Sci Rep. 2018;