

Acrocyanosis, Digital Ischemia and Acronecrosis as First Manifestations of Endometrial Adenocarcinoma: Case Presentation and Literature Review

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Abstract

The association between digital ischemia and cancer is rarely reported in literature and the exact mechanism of this occurrence has not been completely understood. We report here a case of a 73 year-old woman who presented digital ischemia as first manifestation of endometrial adenocarcinoma.

Reporting this rare clinical case and with a brief literature review, we recommend to consider an intensive search for primary and metastatic cancer in all patients who experience a digital ischemia, with the aim to early detect and treat the disease.

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Abbreviations

TBCT: Total Body Computer Tomography; MR: Magnetic Resonance; CytoKAE1/AE3: Cytokeratin AE1/AE3; CitoK7: Cytokeratin 7

CitoK20: Cytokeratin 20; Vim: Vimentin; ECOG PS: Eastern Cooperative Oncology Group Performance Status

Introduction

In 1967 Hawley et al. first systematically reported the association between digital ischemia and malignant disease [1]. In this article the authors described six cases of women suffering from various types of primitive cancer: three women had a primary carcinoma of the kidney, ovary and maxillary antrum respectively; one patient had primary tumor of both the uterus and large bowel; in one case the origin was probably ovarian or pancreatic, while the last case had Hodgkin's disease. In all patients none of the commonly known causes of digital ischemia was present and all women died within a few months after the onset of digital ischemia.

Since then, few other cases have been described in literature, in association with different types of primary tumor [2-19] (Table 1). In the most cases the patients were elderly women with adenocarcinomas of digestive or gynaecologic apparatuses [10,11]. Digital ischemia was often reported bilateral and usually to be preceded by Raynaud's phenomenon [12]. Sometimes the evolution of ischemia followed in parallel the evolution of the tumor [13].

The exact mechanism of this severe occurrence has not been completely understood [14,15] and the available treatment options have an extremely limited utility [13,16,17]. We describe here a new case of acute digital ischemia associated with an endometrial adenocarcinoma in an elderly woman. We also performed a brief review of the literature, in order to evaluate its limited treatment options and to suggest some hypotheses about the possible causes of this rare complication.

Case Presentation

A 73-year-old woman was admitted to our hospital with acrocyanosis of all fingers on both hands. The patient did not complain pain. All the laboratory tests excluded diagnosis of the most common causes of Raynaud's phenomenon and all connective tissue diseases. No vascular risk factor was revealed; her blood pressure was 120/70 mmHg, with a pulse rate of 80 beats per minute. Her weight was stable and she was not diabetic. She referred six months of occasional

Authors	year	Primary neoplasm
Hawley PR et al ¹	1967	Six cases: 1 kidney, 1 ovary, 1 maxillary antrum, 1 both uterus and colon, 1 probably ovary or pancreas, 1 Hodgkin's disease
Andrasch RH et al ¹¹	1976	One case: kidney
Hild DH et al ⁸	1980	One case: chronic granulocytic leukemia
Taylor LM et al ¹⁹	1987	Five cases: 2 breast, 1 kidney, 1 gastric cancer, 1 chronic lymphocytic leukemia
Tolosa-Vilella C et al ¹⁰	1990	One case: unknown primary site
Vowden P et al ¹⁷	1991	One case: breast
Maurice PD ¹³	1996	One case: ovary
Wang HC et al ¹⁶	1996	One case: lung
Chtourou M et al ²	1998	One case: ovary
Legrain S et al ³	1999	One case: ovary
Iamandi C et al ⁵	2002	One case: lung
Wright JR et al ⁸	2002	One case: tonsil
Buch RS ²⁰	2002	mouth floor carcinoma
Kopterides P et al ⁴	2004	One case: lung
Hebbar S et al ⁹	2005	One case: esophagus
Paolini et al ²¹	2009	One case: prostate cancer
Moulakakis K et al ⁶	2010	One case: lung
Robati S et al ⁷	2012	One case: ovary
Onitilio et al ²²	2012	One case: lung
Woei-A-Jin et al ²³	2014	One case: lymphoma
Le Besnerais M et al ²⁴	2014	Cohort of 100 patients with DI, 15% with cancer

Table 1: Digital ischemia and cancer: some reports.

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abdominal pain history. An ultrasound evaluation of abdomen and pelvis was performed revealing the presence of diffuse neoplastic tissue in the uterine cavity. Thus a gynecological examination confirmed an abdominal mass easily bleeding. Endometrial biopsy, Total Body Computed Tomography (TBCT) and abdomen Magnetic Resonance (MR) scan were executed. The imaging did not reveal the presence of distant disease in the lung, liver or brain. Histological findings confirmed an undifferentiated neoplastic tissue. Immunohistochemical examination showed positivity for cytokeratin AE1/AE3 (CitoKAE1/AE3 +) and cytokeratin 7 (CitoK7 +); while it was negative for cytokeratin 20 (CitoK20 -) and vimentin (Vim -). After a multidisciplinary discussion among the surgeon, medical oncologist, gynecologist and radiotherapist, in consideration of the patient's poor Eastern Cooperative Oncology Group Performance Status (ECOG PS = 2) it was decided not to perform hysterectomy and no indication for radiotherapeutic or chemotherapeutic treatment was given. A palliative approach was preferred with the aim to control patient's symptoms. A month later, the physical examination revealed that the acrocyanosis of all fingers was rapidly evolved into distal necrosis on both hands (Figure 1a, Figure 1b). Furthermore the same lesions were also observed on feet fingers (Figure 2). The peripheral pulses were present and there were no other clinical and laboratory findings: full blood count, serum electrolytes, liver function test, glucose, thyroid function tests, were all normal. Moreover antinuclear antibodies and anticardiolipin antibodies were not present. After two months a TBCT showed numerous pathological para-aortic and external iliac lymph-nodes with no evidence of visceral metastatic lesions. Because of the rapid deterioration of clinical conditions, no treatments or other diagnostic procedures were performed. The patient was admitted in a palliative unit and died one month later.

Discussion

The development of digital ischemia in patients with cancer is a very rare event. In their paper, published in 1998, Chtourou et al. [2] reported about 40 cases of digital necrosis associated with different types of primary tumor, described since 1967. Very recently, Le Besnerais and colleagues performed a retrospective study on Digital ischemia associated with cancer (DIAC), reporting that this event is increasing in frequency and more prevalent than previously [24]. They also suggest that when digital necrosis occurs, physicians should be alerted to consider a possible occult malignancy, especially in the presence of age >50 years and thrombocytosis [24]

In many of the reported cases in the literature, as well as in our case, the prognosis is extremely poor. In fact, patients have almost always primary tumor in advanced stage, they present poor clinical conditions and survive only few months after digital necrosis onset [4-9].

Moreover the exact mechanism that leads to the development of ischemia is not known [14,15]. Different pathogenetic processes may be responsible for the phenomenon. All cancers can induce hypercoagulability and increase blood viscosity with various mechanisms (increase of circulating blood cells or proteins) [18]. Moreover tumours can release vaso-constrictive substances [19]. Other processes involved may have immunological origin, for example the creation of antigen/antibody complexes targeted to the vascular endothelium [10,13,15]. Our case, as the cases described in the literature, occurred in women with gynaecological neoplasms [1-3,7,13]. This could be explained by a not yet known interaction of hormonal factors.



Figure 1 (a,b): Acrocyanosis of all fingers, evolved into distal necrosis on both hands.



Figure 2: lesions observed on feet fingers.

It is also interesting to note that in some cases the treatment of primary tumour induced a reduction of the digital ischemia [13,16]. This unfortunately occurs only in a few cases, and obviously the clarification of the pathogenetic mechanism would be important to specifically treat this event.

Many attempts at specific treatment of digital ischemia were made using corticosteroids, immunosuppressive therapies or vasodilators, but usually as in our case, the clinical course is rapidly progressive. However, some partial successes have been obtained with the use of prostaglandin [17], although the way to go to achieve a significant therapeutic benefit is still very long.

Conclusion

In conclusion the aim of this case report is to emphasize that although the prevalence of this occurrence is very low, an intensive search for primary and metastatic cancer is strongly recommend in patients who experience digital ischemia or necrosis, especially in elderly women. In fact, only early diagnosis and prompt treatment of the primary tumor and ischemia may allow better therapeutic results.

Competing Interests

The authors declare that they have no competing interests exit.

Author Contributions

All the authors substantially contributed to the study conception and design as well as the acquisition and interpretation of the data and drafting the manuscript.

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