DIGITAL NECROSIS ASSOCIATED WITH CHRONIC MYELOID LEUKEMIA: A RARE PARANEOPLASTIC PHENOMENON.

L. D'Hondt, Th. Guillaume, Y. Humblet, M. Moriau*, J.M. Lachapelle**, M. Symann.

SUMMARY

We describe the case of a 72-year-old man who developed unilateral digital necrosis, four years after diagnosis of chronic myeloid leukemia (CML). The etiology of this paraneoplastic phenomenon appears multiple. The digital necrosis responded well to an aggressive varied treatment. The unusual association of CML with digital necrosis and the etiology of this rare paraneoplastic complication are discussed.

Acta Clin Belg, 1995; 50-5: 297-300

INTRODUCTION

Digital necrosis is a rare paraneoplastic phenomenon. In most patients, it is associated with hematological neoplasia, rarely with solid tumor. In hematological malignancies, chronic myeloid leukemia (CML) seems to be very infrequently associated with digital necrosis. We report here the case of a patient who developed acute digital necrosis four years after the diagnosis of CML.

CASE REPORT

In 1989, a 68-year-old man was referred for evaluation of fortuitously discovered leucocytosis. His past medical history included only mild hypertension and large bowel diverticulosis. Clinical examination showed mild splenomegaly. Laboratory evaluation revealed a leukocytosis of 24,830 WBC/mm^3 with 75 % neutrophils, 14 % lymphocytes, 5% monocytes and 4% basophils. Platelets were 333,000/mm^3 and hemoglobin was 13.5 g/dl. Buffy coat showed immature granulocytic forms. Serum LDH and uric acid were elevated. Bone marrow biopsy was performed and revealed a typical picture of CML, confirmed by the presence of the Philadelphia chromosome t-(9-22) and low leucocyte alkaline phosphatase. Due to rapid evolution of the disease, treatment with hydroxyurea (Hydrea®) at 1000 mg/day was initiated. Six months later interferon α2A (Roferon®) 3x10^6 units five times a week was added. The disease was adequately controlled during four years, but dose modifications of hydroxyurea were necessary. Repeated bone marrow aspirations confirmed persistence of the histologic and karyotypic abnormalities. At the end of 1993, an ulceration of the left foot appeared. Arterial and venous dopplers were normal. There were no cryoglobulins or cold agglutinins; blood glucose and cholesterol were normal. The clinical presentation suggested vasculitis and interferon was stopped. At the beginning of 1994, the patient presented with several episodes of Raynaud's phenomenon and paresthesia occurring in contact with low ambient temperature, appearing bilaterally and localized on digital extremities. Vasodilatators and anti-aggregant were tried without success. One month later, the patient developed unilateral digital necrosis localized on the ungual phalanx of the medius (Fig 1). Other fingers of the same side and the medius of the opposite were cyanotic but without necrosis. Clinical and laboratory evaluations did not show acceleration of the hematological disease

Services d'Oncologie, d'Hématologie* et de Dermatologie**,
Cliniques Universitaires St. Luc - UCL,
Avenue Hippocrate 10, 1200 Bruxelles

Reprints: Dr. Lionel D'Hondt,
Laboratoire d'Oncologie et d'Hématologie Expérimentales,
54 Avenue Hippocrate, UCL 54.71, 1200 Brussels

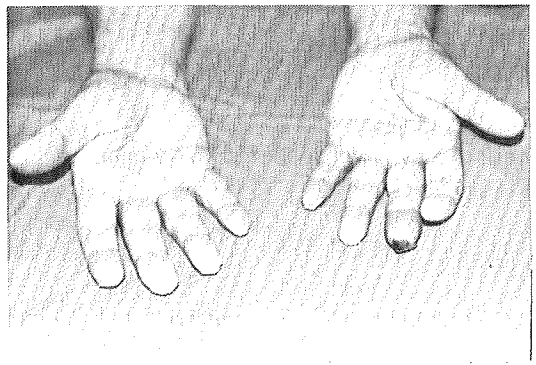

Fig. 1: Digital necrosis of the left ungual phalanx of the medius. Other fingers of the same hand and the medius of the opposite were cyanotic but not necrotic.

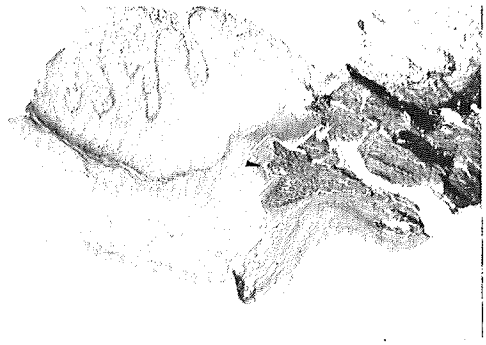

Fig. 2 a, b: H. E. stain x25 and x250. The anatomopathologic picture of the finger skin biopsy displays steep side ulceration. Where epiderm is interrupted, within parakeratosic corneus lamella, a large collection of neutrophils is visible (arrow).

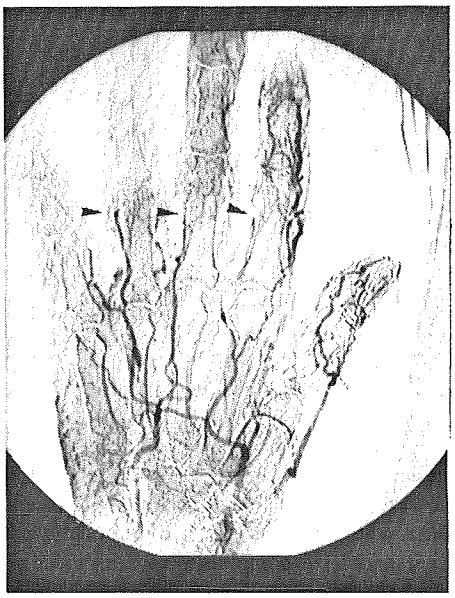

Fig. 3 Angiography of the left hand showing complete block at the digital arteries of the 2nd, 3rd, 4th and 5th fingers (arrows).

or the presence of inflammatory process. No sign of systemic sclerosis was present. WBC was 17,730/mm^3 and platelets 559,000/mm^3. Bacterial, viral, autoantibody serologies including anti-cardiolipin and Coombs' reaction were negative. Serum complement was normal. There were polyclonal increases of both serum IgA and IgG with a blood hyperviscosity of 9 centipoises (N: 4-8) but again without cold agglutinin or cryoglobulin. Platelet aggregation tests were normal, respectively 56 % for ADP and 78 % for collagen. β-thromboglobulin (87 ng/ml- N:15-40) and platelet factor 4 (PF4) (12 ng/ml- N: 4-10) levels were elevated indicating platelets activation. EKG was normal. Skin biopsy showed steep side ulceration with pericapillar leucocytoclasic infiltrations and a large collection of neutrophils, but no neoplastic emboli or thrombi (Fig.2). Immunostaining showed C3 deposits in the vessel wall of the deep and intermediate derm. The picture was characteristic of acute vasculitis. Angiography of the left hand showed complete arterial blocks localized in the digital arteries of the 2nd, 3rd, 4th and 5th fin-

gers (Fig 3). Capillaroscopy displayed megacapillars. Oral methylprednisolone (Medrol®) 1 mg/kg/day, ticlopidine (Ticlid®) at 500 mg/day and nadroparine (Fraxiparine®) subcutaneously at 7,500 U/day were begun. After 3 months of treatment, the digital necrosis resolved and the methylprednisolone was progressively discontinued. Currently, the hematologic disease remains stable. Unfortunately, 8 weeks following discontinuation of corticosteroids the lesions recurred with involvement of the right hand. Upon readministration of steroids, we again observed a major improvement of the cutaneous lesions.

DISCUSSION

Digital necrosis is a rare paraneoplastic phenomenon. To date, 26 cases have been reported (1). In most of the cases, digital necrosis was associated with hematological malignancies (most frequently in acute leukemia and hairy cell leukemia) and only rarely with solid tumors (1,2). To our knowledge, the present case is only the third in which a digital necrosis has been described in a patient with CML (3,4). Digital necrosis is generally bilateral, symmetric and involves the upper extremities (3). In our patient, digital necrosis probably resulted from a combined etiology including vasculitis, hyperviscosity, and platelet activation inducing a complete vascular block. Vasculitis seemed to be the most important mechanism. Vasculitis is associated mainly with hematologic disorders such as hairy cells leukemia, acute leukemia and myeloproliferative disorders (3,5,6). Three case reports of CML associated with vasculitis have been reported (6). It may be associated with a Raynaud's phenomenon. Usually autoantibodies, viral serology and complement levels are unremarkable. The vasculitis is classically localized in medium and small arteries, and the histopathologically commonest form is leukocytoclastic. Immunofluorescent staining for IgG, IgA, IgM, C3, C4 and fibrin are usually negative. Mechanisms for the induction of paraneoplastic vasculitis are at least three fold:

1) Formation of immune complexes of tumor-associated antigens or antibodies;
2) Vascular lesions by antibodies directed against endothelial cells;
3) Direct effect of cancer cells and chemotherapy on the vascular wall (7).

Leukemic or malignant cells have not been identified in any skin biopsy specimens (3). Nonsteroidal anti-inflammatory agents and chemotherapeutic agents are uniformly unsuccessful, but some patients respond to corticosteroid treatment. Isolated paraneoplastic vasculitis rarely leads to digital necrosis. The second mechanism that could contribute to the pathogenesis of the digital necrosis was hyperviscosity. Hyperviscosity has rarely been described in CML (8). One case has been reported in which hyperviscosity was due to leucostases secondary to a very high WBC and a direct correlation between white cell count and viscosity was found (8). In our case, hyperviscosity was mild but detectable and leucocytosis was well controlled by hydroxyurea. In some cases, hyperviscosity may be caused by increased circulating blood proteins or cryoglobulins. In their report, Hild and Myers described a complete remission of lesions after diminution of WBC count (8). Platelet activation and thrombocytosis could be the third mechanism involved in our patient. Hypercoagulability (which was not present in our case) and thrombocytosis are fairly frequent in malignant tumors and in some cases clinically relevant. Myeloproliferative syndromes are likewise associated with hypercoagulability status. Usually, there is a relative resistance to treatment of this form of hypercoagulability (2). In some cases, arterial occlusion is directly caused by leukemic blast cells thrombi (9).

In conclusion, we believe that digital artery occlusion seen in our patient can be caused by the three concomitant mechanisms of arteritis, platelet activation and hyperviscosity. Arteritis seemed predominant. Digital necrosis associated with malignancy is a rare paraneoplastic

phenomenon (1,4). It must be noticed that this paraneoplastic phenomenon occurred with a seemingly stable hematologic disease. This is probably due to the fact that in CML there is a permanent production of neoplastic blast cells. No additional clinical entities other than CML itself were identified to explain digital necrosis and in particular, the role of interferon α2A seems unlikely. Treatment was aimed at two mechanisms and included platelet anti-aggregant, anticoagulant drugs, and high-dose oral corticosteroids. As a result of treatment, digital lesion and cyanosis dramatically improved within three months. Unfortunately, lesions recurred necessitating to restart methylprednisolone.

RESUME

Nous décrivons le cas d'un homme de 72 ans qui développe une nécrose digitale unilatérale quatre ans après le diagnostic de leucémie myéloïde chronique (LMC). L'étiologie de cette nécrose digitale semble multiple. Elle a bien répondu à un traitement varié et agressif. Nous discutons la rareté et l'étiologie de l'association LMC et nécrose digitale.

SAMENVATTING

Wij beschrijven het geval van een man van 72 jaar die een unilaterale digitale necrosis ontwikkeld vier jaar na de diagnosis van chronische myeloid leukemie (CML). De etiologie van deze digitale necrosis schijnt meervoudig te zijn. Deze heeft goed op een agressieve en gevariëerde terapie gereageerd. Wij bespreken de zeldzaamheid en de etiologie van de associatie van CML en digitale necrosis.

ACKNOWLEDGMENT

We wish to thank Gilda Manicourt for her secretariat assistance in preparing the manuscript.

REFERENCES

1. Petri M, Fye K. Digital necrosis: A paraneoplastic syndrome. *J Rheumatol.* 1985; 12: 800-2.
2. Taylor L, Hauty M, Edwards J, Porter J. Digital ischemia as a manifestation of malignancy. *Ann Surg.* 1987; 206: 62-8.
3. Mertz L, Conn D. Vasculitis associated with malignancy. *Curr Opin Rheumatol.* 1992; 4: 39-46.
4. Vayssairat M, Fiessinger J, Bordet F, Housset E. Rapports entre nécroses digitales du membre supérieur et affections malignes. *Nouv Presse Méd.* 1978; 7: 1279-82.
5. Longley S, Caldwell J, Panush R. Paraneoplastic vasculitis. Unique syndrome of cutaneous angiitis and arthritis associated with myeloproliferative disorders. *Am J Med.* 1986; 80: 1027-30.
6. Greer J, Longley S, Edwards L, Elfenbein G, Panush R. Vasculitis associated with malignancy. Experience with 13 patients and literature review. *Medicine.* 1988; 67: 222-30.
7. Brooks P. Rheumatic manifestations of neoplasia. *Curr Opin Rheumatol.* 1992; 4: 90-3.
8. Hild D, Myers T. Hyperviscosity in chronic granulocytic leukemia. *Cancer.* 1980; 46: 1418-21.
9. Fass R, Zaizov R, Sandbank Y et al. Recurrent peripheral arterial occlusion by leukemic cells sedimentation in acute non myelocytic leukemia. *J Ped Surg.* 1992; 27: 665-7