Eur J Vasc Endovasc Surg **22**, 474–476 (2001)
doi:10.1053/ejvs.2001.1454, available online at http://www.idealibrary.com on IDEAL®

CASE REPORT

Interferon Induced Severe Digital Ischaemia in Chronic Myeloid Leukaemia – Successful Treatment Using Ketanserin

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Key Words: Ketanserin; Digital ischaemia; Interferon; Chronic myeloid leukaemia.

Introduction

Interferon (IFN) has an established place in the treatment of chronic myeloid leukaemia (CML) achieving a haematological response in 60–80% of patients and significantly longer survival than that following conventional chemotherapy alone.[1] Adverse effects, often dose dependent, include a self-limiting flu-like illness, thyroid dysfunction, lupus-like syndrome and Raynaud's phenomenon.

A patient with CML who sustained severe digital ischaemia of both hands attributable to IFN therapy and who benefited from ketanserin therapy is reported.

Case Summary

A 27-year-old female with no cardiovascular risk factors was referred with advanced digital ischaemia of both hands. She originally presented with a profound normocytic normochromic anaemia (Hb 6.2 g/dl), marked thrombocytosis (platelets 2273×10^9/l) with platelet anisocytosis, giant platelets and occasional blasts. Bone marrow aspiration, trephine biopsy and bone marrow cyogenetics confirmed Philadelphia chromosome positive CML (BCR/ABL fusion gene detected by RT PCR). Treatment with hydroxyurea was initiated to control the platelet count and subsequently subcutaneous IFN (Interferon Alpha-n1 Wellferon) in accordance with the MRC CML 4 trial protocol.

Following 12 weeks of IFN therapy she presented with severe digital ischaemia of both hands and distressing throbbing pain necessitating 400 mg morphine sulphate daily. The tips of the digits were nonviable, ulcerated and infected (Fig. 1A). Upper limb pulses were all palpable. Autoimmune (including anti-ds DNA, cryoglobulins), coagulation and thrombophilia screens were all negative or within normal range. Subclavian angiography revealed uneven obstruction of the digital arteries (Fig. 1B).

Intravenous ketanserin was commenced and 48 h later dextran 40, enoxaparin and aspirin added; cephaclor was started to counter infection and hydroxyurea continued. Within 3 weeks of intravenous ketanserin therapy, flow to the digits assessed by Doppler had reverted to normal, the fingers began to heal, and her analgesic requirements decreased. A month later debridement resulted in excellent preservation of the finger tips. She underwent successful bone marrow transplantation and remained on oral ketanserin 40 mg bd for 6 months after discharge.

Discussion

Raynaud's phenomenon, a known side effect of IFN therapy,[2] represents either an exacerbation of preexisting autoimmune disease or a direct unknown vasospastic effect. Arteriographically documented digital artery occlusions causing finger tip necrosis are

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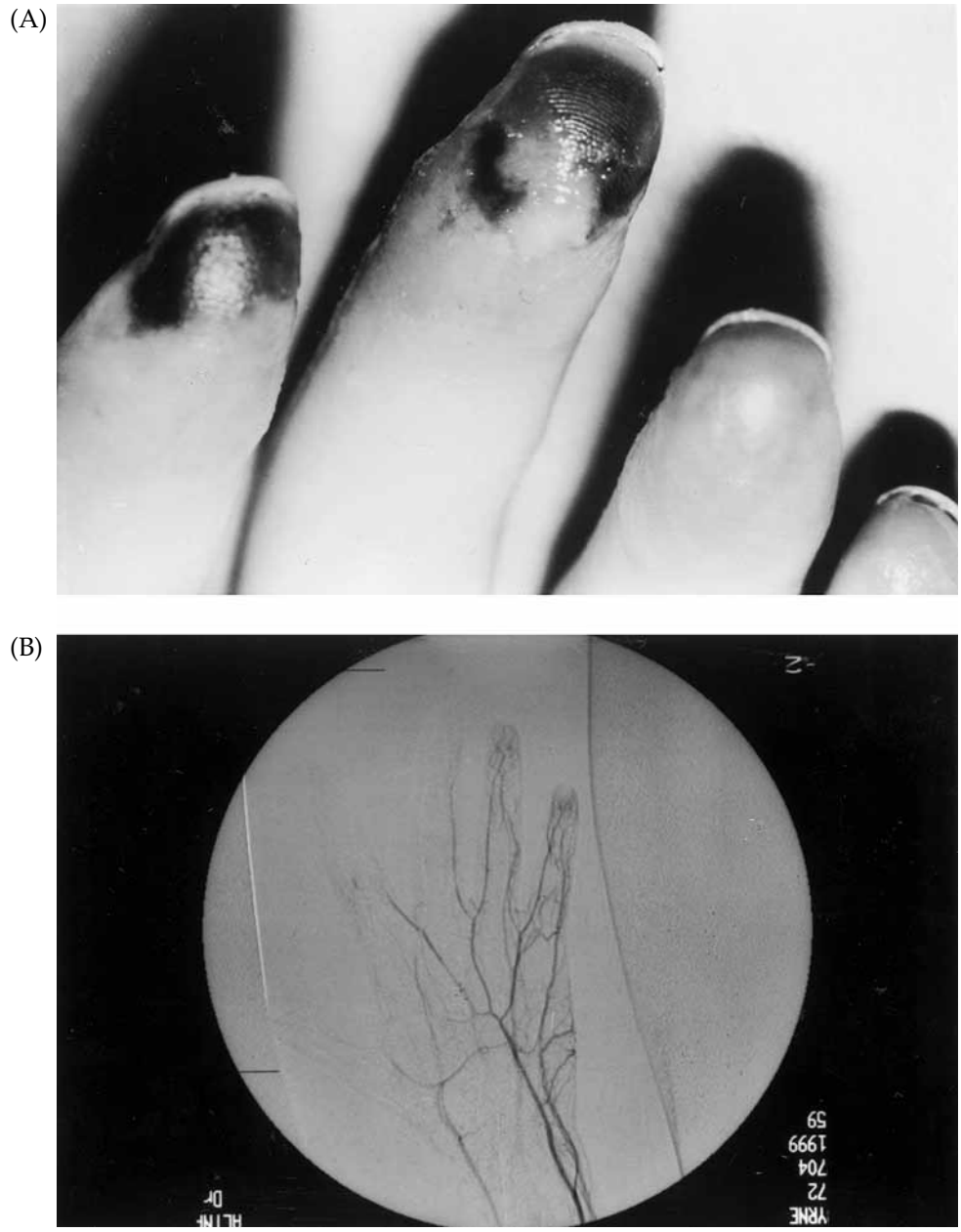

Fig. 1. (A) Pre-treatment photograph demonstrating Interferon induced severe digital ischaemia. (B) Palmar arch arteriogram illustrating uneven obstruction of digital arteries.

a new and rare finding[2]. Necrotising vasculitic skin reactions occurring in CML patients on IFN are independent of IFN type, administration modality, duration of therapy, stage of disease and cytogenetic response to treatment.[3]

Platelet activation following vascular injury results in release of endogenous agonists such as serotonin, ADP and thromboxane A_2 which accelerate the formation of platelet aggregates and induce vasoconstriction.[4] The platelet plug and damaged endothelium release vasoactive substances which trigger the clotting cascade causing microcirculatory thrombosis and ischaemia of peripheral tissues.

Neither CML nor the drugs administered are known to induce vasospastic disorders[5] and the platelet count in this patient remained normal. Hence it would be

reasonable to conclude that digital artery occlusion is a rare side effect of IFN therapy, and in such circumstances should be stopped.

Serotonin modulates the contractile activity of vascular smooth muscle cells (VSMC) and activation of serotonergic 5-HT_2 receptors causes vasoconstriction. Serotonin also activates platelets and *in vitro* induces shape change and weak reversible platelet aggregation.[4]

Ketanserin is a selective antagonist of the 5-HT_2 serotonin receptor devoid of partial agonist properties and has moderate alpha-1 adrenergic receptor blocking effects.[4] It inhibits serotonin induced platelet aggregation and also prevents vasoconstriction in a dose-dependent manner.[3,4] The efficacy of ketanserin in reversing the ischaemia and preserving the viability of the digits was clearly observed in this case.

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