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Chronic neutrophilic leukaemia

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ABSTRACT

Chronic neutrophilic leukaemia is a rare myeloproliferative disease characterised by splenomegaly, sustained neutrophilia, raised vitamin B12 level and absence of the Philadelphia chromosome. We report a 74-year-old man who presented first with Sweet's syndrome and subsequently leukocytosis. He had splenomegaly, a raised vitamin B12 level, serum uric acid and neutrophil alkaline phosphatase score. Cytogenetic study of the marrow was normal and peripheral blood for BCR-ABL gene transcript was not detectable. He subsequently passed away with bronchopneumonia.

Keywords: chronic neutrophilic leukaemia, leukaemia, neutrophilia, Sweet's syndrome

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INTRODUCTION

Chronic neutrophilic leukaemia (CNL) is a rare BCR-ABL negative myeloproliferative disorder which is characterised by persistent mature neutrophilia, raised serum vitamin B12, raised neutrophil alkaline phosphatase (NAP), hepatosplenomegaly and raised serum uric acid.[1] It generally affects both sexes and is usually seen in the elderly population. Most patients have a poor prognosis, with a median survival of less than three years.[2] Management is usually symptomatic although in younger patients, allogeneic transplantation may be a curative therapy option. We report an elderly patient with CNL who presented initially with neutrophilic dermatits on both of his hands.

CASE REPORT

A 74-year-old Chinese man was first seen by a dermatologist with a five-month history of multiple raised skin lesions on both his palms and hands. A biopsy of the skin lesion two months before attending the haematology clinic showed chronic nonspecific dermatitis. He was treated with steroid cream with minimal response. He was later referred to us when routine blood counts showed a raised white cell count (TWC) of 79.3 × 10^9/L. He denied any other constitutional symptoms except for weight loss of three kg in the past six months. He had vitiligo since 1998 and felt that it had gotten worse in the past year.

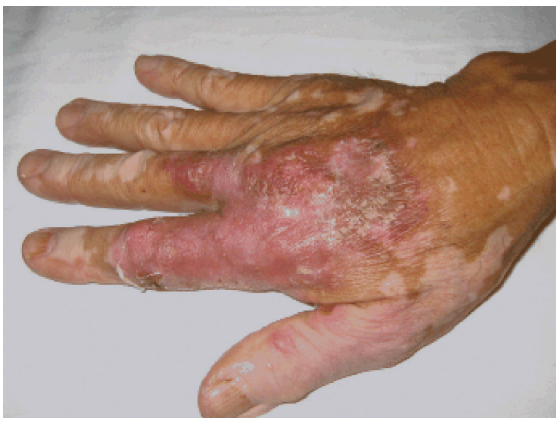

Fig. 1 Photograph shows skin lesions of the hand.

There was no other significant past history except two years ago, when he was told by his general practitioner that he had vitamin B12 deficiency anaemia and was given methylcobalamin injections. His haemoglobin (Hb) level improved, and incidentally it was noted that his TWC was slightly raised at that time but no further investigations were performed. He denied taking any medications.

On presentation, he appeared well and was afebrile. There was hepatosplenomegaly but no palpable lymphadenopathy. On both of his hands and palms, there were several patches of raised, scaly, violaceous skin lesions with some areas of erythema (Fig. 1). No other abnormal physical findings was noted. Laboratory investigations showed a Hb level of 110 g/dL, TWC of 79.3 × 10^9/L with 89% neutrophils and a platelet count of 291 × 10^9/L. Peripheral blood film showed leucocytosis with increased segmented and band stages of neutrophils. A few myelocytes and an occasional blast was noted.There was no basophilia or eosinophilia. Serum electrolytes were normal except for a mild renal impairment (Cr 191 μmol/L). Lactate dehydrogenase was high at 421 IU/L. Serum assay showed a raised ferritin level (450.7 μg/L) and a raised vitamin B12 level (1,239 pmol/L). Serum uric acid was raised (598 μmol/L).

Ultrasonography of the abdomen did not show any abnormality except for an enlarged spleen. Chest radiograph was normal. Thyroid function test was normal and tumour marker studies including alpha-foetal protein and prostatic specific antigen were not increased. A repeat skin biopsy showed infiltration

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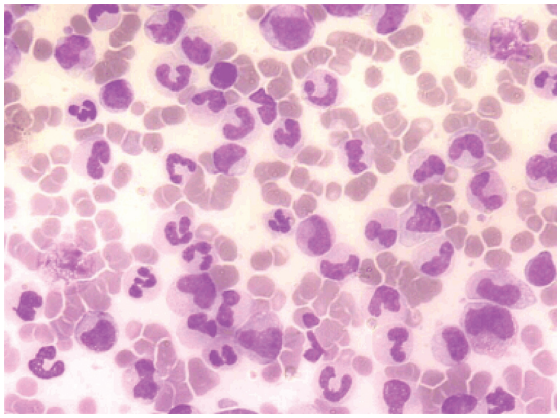

Fig. 2 Photomicrograph of bone marrow aspirate shows neutrophilia (May-Graunwald Giemsa, x400).

of neutrophils in the subepidermal area with some perivascular inflammatory aggregates. Periodic acid-Schiff stain showed preservation of basement membrane and no fungal or epithelioid granuloma was found. A diagnosis of neutrophilic dermatosis was made. Bone marrow aspirate showed a hypercellular marrow with marked granulocytic proliferation, consisting mainly of stab forms and segmented neutrophils (Fig 2). Dysplastic features were noted in the granulopoeitic precursors. There was no increase in basophils and eosinophils. Erythropoiesis was depressed. Trephine biopsy showed a similar picture and there was no increase in reticulin fibres. Cytogenetics were normal. Real-time polymerase chain reaction (PCR) was performed using sequence specific primers and TaqMan probes[3] for amplification and detection of BCR-ABL (b3a2, b2a2, e1a2, e19a2) on the peripheral blood, confirming the absence of BCR-ABL fusion gene transcripts for the p230,[4] p210 and p190 BCR-ABL proteins. The NAP score was raised. Serum immunoglobulins were normal with no abnormal monoclonal protein.

In view of his age and absence of other possibilities of neutrophilia, a diagnosis of CNL was made. Hydroxyurea was started to control the blood counts. His skin lesion improved a month after treatment. The patient refused further treatment with interferon. Three months after his initial presentation to the unit, he developed a right deep vein thrombosis (DVT) involving the superficial femoral vein and extending to the right popliteal vein. There was no obvious precipitating factor. Oral anticoagulant was started and that was continued for a total of six months with no major adverse events. Thrombophilia screen which included antithrombin, protein C and S assays were normal. His blood counts remained stable with low dose of hydroxyurea.

Nine months after his presentation, his blood counts deteriorated, with persistent anaemia which required frequent red cell transfusion. The TWC was difficult to control and was persistently above 100 × 10^9/L and majority of the cells were neutrophils. There was also persistent thrombocytopenia. A repeat bone marrow aspirate showed a hypercellular marrow with blast counts of 5% and a reduction in megakaryocytes. The spleen had also increased in size. Subcutaneous interferon alpha 5 MU three times a week was started. Unfortunately, his counts remained difficult to control after a month of interferon, with Hb level persistently less than 8 g/dL and platelet count less than 20 × 10^9/L. Interferon was stopped and his raised TWC was again controlled by hydroxyurea. He finally developed bronchopneumonia and passed away about a year after his first presentation.

DISCUSSION

Neutrophilia is a common encounter in normal clinical practice. Infections remain one of the major causes of neutrophilia. Other conditions which are associated with neutrophilia are chronic inflammatory conditions and occult malignancy. Drugs such as glucocorticoids, lithium and granulocyte colony stimulating factors can also raise neutrophil count which generally resolves after withdrawal of the specific drug. Once all other causes are excluded, haematological causes such as chronic myeloid leukaemia or CNL should be entertained.

CNL is a rare myeloproliferative disorder and it should be a diagnosis of exclusion. Although CNL was first described in 1920 by Tuohy, not much is known about its pathogenesis and treatment.[2] CNL is characterised by persistent mature neutrophilia, splenomegaly, raised vitamin B12, raised NAP score, with no evidence of basophilia and the absence of BCR-ABL transcripts.[2]

CNL can only be confidently diagnosed by careful exclusion of the presence of BCR-ABL gene transcript associated with chronic myeloid leukaemia and other diseases which may cause a leukaemoid reaction e.g. occult malignancy, ongoing infections and other inflammatory conditions. In our patient, there was no evidence of infections and underlying malignancy was also excluded with the absence of symptoms and signs as well as the normal radiological findings.

Chronic myeloid leukaemia has to be excluded in our patient especially with the presence of hepatosplenomegaly by detection of BCR-ABL fusion gene. Various assays are available for detection of BCR-ABL fusion gene such as cytogenetic, fluorescent in-situ hybridisation, southern blotting for detection of the rearrangement of the BCR gene within the breakpoint cluster region, and western blotting to detect the BCR-ABL oncoprotein. However, PCR remains the most sensitive method for detection of known

mutation. Real-time PCR has great advantages for detection of BCR-ABL transcripts in terms of sensitivity and rapid assay time. An atypical BCR-ABL fusion gene transcript involving the c3/a2 junction, which is now known as e19a2, has been described in Ph+ patients with clinical findings of CNL.[4] In our patient, we were able to confidently exclude the presence of BCR-ABL fusion gene by both cytogenetic and real time PCR.

Myelodysplastic syndrome can sometimes be associated with neutrophilia although one would expect dysplastic features in other cell lines and abnormal cytogenetic findings in the marrow. The significant organomegaly is also unlikely to occur in myelodysplastic syndrome.

There have been reports of raised neutrophil counts in association with plasma cell dyscrasias, such as monoclonal gammopathy of unknown significance (MGUS) or multiple myeloma (MM). This could be a reactive phenomenon and the prognosis is better in MGUS than MM.[1] There was no evidence of paraproteinaemia in our patient. Cutaneous involvement is relatively common in leukaemia although in CNL, it is rarely reported. Nonspecific dermatoses like Sweet's syndrome can occur in 30% of leukaemia patients.[5] There has been to date one case report of a patient with CNL presenting with leukaemia cutis,[5] and another case presenting with neutrophilic dermatoses.[6] In our patient, there is no evidence of leukaemia cutis but reactive neutrophilic dermatoses which subsequently resolved with hydroxyurea.

True CNL usually affects the elderly and the median age at presentation is 62.5 years.[1] The median survival ranges from 21 months to 30 months, with about 28% overall survival at five years.[1,2] Most patients present with normal Hb level and platelet counts of less than 100 $\times 10^9$/L is rare. All patients present with raised TWCs (range, 10–172 $\times$ 10^9/L) with mainly segmented and band stages of neutrophils.[1] Myelocytes and metamyelocytes are infrequently seen. Serum vitamin B12 and uric acid levels are uniformly raised. The NAP score is usually elevated. Bone marrow aspirate findings were uniformly hypercellular with marked granulocytic proliferation showing no abnormal distribution pattern.[1] Low serum granulocyte-colony stimulating factor (G-CSF) has been documented suggesting that neoplastic granulopoeisis has a suppressor effect on G-CSF synthesis.[1] Cytogenetic abnormalities have been associated with 37% of CNL cases and the abnormalities include trisomy 8, trisomy 21, del(20q) and t(1;20).[1]

Experience in treatment of CNL is limited due to its rare incidence. Optimal therapy is unclear and is mainly for symptomatic support. Oral chemotherapeutic agents, e.g. busulphan and hydroxyurea are useful in controlling the high white cell counts but it is by no means curative. Splenectomy or splenic irradiation has been used and found to be effective in reducing symptomatic splenomegaly although this may aggravate neutrophilia.[1] Other treatments, e.g. alpha-interferon, have been used with some success to reduce the tumour burden without suppressing normal haematopoeisis.[2] In view of the aggressive nature and possible leukaemia transformation from CNL, bone marrow transplants should be an option for younger patients with a suitable donor. In view of our patient's age, symptomatic control was the aim and unfortunately, this became difficult to achieve and he finally passed away one year after diagnosis. In summary, CNL is a distinct disease which must be distinguised from CML and the more common leukaemoid reaction. Treatment remains challenging due to the relative old age at presentation and the limited cases available for clinical trials.

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