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PARANEOPLASTIC RHEUMATIC DISORDER IN ACUTE LEUKAEMIA: DIAGNOSTIC CONUNDRUM.

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ABSTRACT

The association of paraneoplastic rheumatic disorder and acute lymphoblastic leukaemia is rarely reported in the adolescent male. The clinical manifestations develop within two years before the diagnosis of associated malignancy. We report a case of an 18-year-old male, who presented with pyrexia of unknown origin, bicytopenia and autoantibodies that was consistent with the diagnosis of systemic lupus erythematosus. The peripheral blood film was eventually consistent with pancytopenia, devoid of any dysplastic changes or abnormal cells. When his cytopenia persisted despite empirical steroid therapy, a trephine biopsy revealed a diagnosis of acute lymphoblastic leukaemia. He was started on chemotherapy with UKALL regime and was well in his recent follow-up early this year where he was on maintenance therapy.

Keywords: Acute lymphoblastic leukaemia, Autoimmune, Paraneoplastic syndrome, Rheumatic disorder, Systemic lupus erythematosus.

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ABSTRACT

The association of paraneoplastic rheumatic disorder and acute lymphoblastic leukaemia is rarely reported in the adolescent male. The clinical manifestations develop within two years before the diagnosis of associated malignancy. We report a case of an 18-year-old male, who presented with pyrexia of unknown origin, bicytopenia and autoantibodies that was consistent with the diagnosis of systemic lupus erythematosus. The peripheral blood film was eventually consistent with pancytopenia, devoid of any dysplastic changes or abnormal cells. When his cytopenia persisted despite empirical steroid therapy, a trephine biopsy revealed a diagnosis of acute lymphoblastic leukaemia. He was started on chemotherapy with UKALL regime and was well in his recent follow-up early this year where he was on maintenance therapy.

Keywords: Acute lymphoblastic leukaemia, Autoimmune, Paraneoplastic syndrome, Rheumatic disorder, Systemic lupus erythematosus.

INTRODUCTION

Paraneoplastic rheumatic disorder (RD) is a disorder in which patients experience rheumatic symptoms that coincide or precede the diagnosis of malignancy.[1] The symptoms may develop within two years before the diagnosis of associated malignancy is discovered.[2] The clinical manifestation involves joints, muscles, bones and vessels.[3] It is commonly unresponsive to conventional treatments while mostly improving with the treatment of the underlying malignancy.[1]

Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystem involvement. European League Against Rheumatism (EULAR) and the American College of

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Rheumatology (ACR) has published new criteria for classification for SLE in 2019.[4] Based on these criteria, an antinuclear antibody (ANA) titre of at least 1:80 must be present at least once. Another 22 criteria subdivided into seven clinical domains and three immunologic domains, and a score of 10 or more is considered consistent with SLE. Secondary HLH can occur in SLE patients, which is suspected especially when the patient has prolonged fever, hepatosplenomegaly, pancytopenia, and elevated levels of liver enzymes, triglyceride, and ferritin, despite adequate treatment for SLE. Haemophagocytic lymphohistiocytosis (HLH) is an immune activation of T cells and macrophages leading to multi organ involvement.[5] However, diagnosis of SLE in males is rare. Subsequent tendency to develop HLH is even rarer, with a reported prevalence of 0.9% to 4.6%.[6]

Most paraneoplastic RD is difficult to differentiate from idiopathic autoimmune disorders; thus, the primary malignancy may cause a significant diagnostic challenge. This may contribute to delay in detection and treatment. Therefore, this case illustrates paraneoplastic RD in acute lymphoblastic leukaemia, which contributed to the diagnostic conundrum.

CASE REPORT

An 18-year-old male presented with prolonged fever for three months. He has on and off ankle, finger, wrist and shoulder joints pain, but denied joint swelling or stiffness. It was associated with lethargy and loss of weight (three kilograms in one month). There was no sore throat, shortness of breath, chest pain, hair loss, abdominal pain, night sweats or history of travelling. His father has psoriasis. However, there was no family history of malignancy or blood disorders. He is the second out of a quadruplet. All his six siblings were healthy. Clinical examination revealed pallor but no jaundice, nor enlarged lymph nodes. There were no oral ulcers, joint swellings, or bruises. Abdominal examination revealed no hepatosplenomegaly. Examinations of other systems, including central nervous system examination, were unremarkable.

Haemogram revealed pancytopenia, with a white cell count of 1.02 x 10^9/L, haemoglobin of 8.6 g/dL and platelet of 137 x 10^9/L. Peripheral smear showed presence of both microcytes and macrocytes. There was no circulating abnormal mononuclear or blast cell. Serum ferritin was 7707ng/ml, with low serum iron (7.9 umol/l) total iron-binding capacity (32.5 umol/l). His serum folate and serum B12 were normal. Erythrocyte sedimentation rate (84 mm/hr) and C-reactive protein (22 mg/L) were high. Viral infective screening, including hepatitis B, hepatitis C and human immunodeficiency virus, were negative. Renal and liver enzymes were normal. Lactate dehydrogenase (LDH) was high. Other investigations were as in Table I. His clinical and laboratory findings were consistent with SLE, fulfilling entry criterion and scoring 21 for additive criteria of the EULAR/ ACR Classification Criteria for SLE (fever, leukopenia, thrombocytopenia, multiple joint pain, and anti-smD1 antibody).

Table I: The immunological profile, lactate dehydrogenase and thyroid function test result.

Test	Results
C3	1.06 g/L
C4	0.41 g/L
ANA	Positive (1:80)
dsDNA	<50
Anti- smD1	Positive
RF	21 IU/ml positive
ENA	All negative
Beta 2GPI	Negative
Anti-cardiolipin	Negative
NK cell count	Decrease in total T cells. Decrease in absolute count of helper T cells, cytotoxic T cells, B cells and NK cells. Suggestive on the immunosuppressed state.
T cells	
B cells	
TFT	Normal
LDH	668

TFT: thyroid function test; LDH: lactate dehydrogenase; ANA: antinuclear antibody

He was treated with hydrochloroquine 200mg OD and prednisolone 30 mg OD However, there was not much clinical (fever continued to persist) and haematological improvement after one month of treatment. He had an on and off spiking temperature despite the treatment. Because of the high serum ferritin, secondary haemophagocytic lymphohistiocytosis (HLH) was considered, and his marrow was studied. Marrow aspirate was dry and trephine biopsy (Figure 1) showed an increase in immature cells, which were moderate to large in size, high nuclear to cytoplasmic ratio, irregular nuclei outline, open chromatin, and prominent nucleoli. These immature cells were positive for cluster of differentiation (CD) 34, terminal deoxynucleotidyl transferase (TdT), Pax-5 and CD79a, and were negative for myeloperoxidase (MPO) and CD117. They were arranged in clusters and dispersed singly. The tumour cells were also admixed with the reactive small lymphocytes in the lymphoid follicles. There was reduced granulopoiesis. The megakaryocytes were arranged in a loose cluster and exhibited reactive changes with dysmegakaryopoiesis. The trephine biopsy was concluded as acute lymphoblastic leukaemia B-lineage (based on WHO classification), with a background of reactive marrow. The cytogenetic study was normal. He was treated with chemotherapy with UKALL regime.

He was last reviewed in January 2024 in our outpatient clinic and is currently still on maintenance chemotherapy for his leukemia.

DISCUSSION

This case illustrates that rheumatic manifestations dominated in acute lymphoblastic leukaemia (ALL). The malignancy typically develops within two years of rheumatism diagnosis, as in this patient, he was diagnosed with ALL after three months of clinical presentation.[2] Even though the pathogenesis is not clear, some scientist postulates the involvement of immune mediators such as hormones, antibodies, cytokines, peptides and cytotoxic T-lymphocytes play an important role in the development of this disorders.[7] Yao *et al*., suggested there may be a relationship between increased interleukin-6 (IL-6) activity in SLE and the increased risk of haematological malignancies.[8]

Bacteria, viruses, or radiation may trigger paraneoplastic disorder and malignancy, leading to the release of hormones and peptides by tumour cells which trigger inflammation. Hypersensitivity reaction develops in response to intracellular antigen released from tumour cells, which produce autoantibody towards nuclear proteins.[9] A study showed a higher percentage of male patient involvement (57%), with a mean age of 62.4±14.2 years.[10] In the study, they speculate that rheumatoid arthritis (RA) in males may give high suspicion of cancer polyarthritis, as the autoimmune disease is more common in females.

The initial diagnosis of SLE was made based on EULAR/ACR criteria and positive anti-smD1, which is specific for SLE. However, since SLE rarely occurs in males, the treating physician decides to look for other diagnoses such as haematological malignancy and chronic infection. SLE itself has been reported to elevate the malignancy risk, such as non-Hodgkin's lymphoma and acute leukaemia.[11,12] On the contrary, there is evidence to suggest that the malignancy is detected following SLE treatment, which is unlikely in this case, due to very short treatment exposure. Another study reported no association between the cancer risk and the use of systemic glucocorticoid, cyclophosphamide, methotrexate, or azathioprine. They concluded that hydroxychloroquine was negatively associated with cancer risk in SLE patients.[13]

The patient was also investigated for the possibility of haemophagocytosis since he had three out of eight criteria for HLH: fever, pancytopenia, and high serum ferritin level. In SLE, acquired HLH may develop, triggered by various conditions such as infections, autoimmune diseases, and malignant tumours.[14] New diagnostic criteria were developed in 2004. The diagnosis is made when more than five of the eight criteria were fulfilled.[15]

ALL is common haematological malignancy in children and it can manifest with musculoskeletal symptoms. However, the paraneoplastic RD also have a wide spectrum of clinical manifestation, which can mask the underlying pathology. The patient may manifest as arthritis, myositis, lupus-like syndrome and vasculitis, which adds to the conundrum in making making a correct diagnosis.

CONCLUSIONS

Rheumatic disease in a male patient should alert the clinician to look for an underlying malignancy. Improving our understanding of paraneoplastic rheumatic disorders in malignancy may avoid misdiagnosis and delay in treatment as early detection and therapy is of utmost clinical importance.

DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest in preparation, or publication of this manuscript.

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