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Extreme leucocytosis: not always leukaemia

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ABSTRACT

Three patients were analysed for an extreme leucocytosis (>50 x 10^9/l) because leukaemia was suspected. In all three patients the leucocytosis proved to be caused by a leukaemoid reaction. This reaction was associated with a hepatic angiosarcoma in the first patient, with a *Salmonella* infection in the second patient and with a necrotic leg abscess in the third patient. Retrospectively, 25 patients with a leukaemoid reaction were identified in our hospital during a four-year period. Besides leukaemia, a leukaemoid reaction, which often has a dismal prognosis, should be considered in patients with an extreme leucocytosis.

KEYWORDS

Leucocytosis, leukaemoid reaction, paraneoplastic

INTRODUCTION

The causes of leucocytosis include severe infection, a (haematological) malignancy or use of certain drugs such as G-CSF (granulocyte colony-stimulating factor). A leucocyte count exceeding 50 x 10^9/l could be due to leukaemia or a leukaemoid reaction.[1] In a recent case report in the Netherlands Journal of Medicine, a patient was presented with a leukaemoid reaction in metastasised melanoma.[2] In this report, we describe three patients with an extreme leucocytosis associated with a malignant or infectious disease. Besides, we report the results of a retrospective study on the incidence and causes of possible leukaemoid reactions in a large teaching hospital during a four-year period.

CASE REPORTS

Patient A, a 74-year-old man, visited the Emergency Department because of progressive jaundice and fatigue. For four weeks he had experienced an intermittent fever of up to 38.5°C and upper abdominal discomfort. He had lost 8 kg in weight. Previous medical history revealed surgery and radiation therapy for cystic carcinoma 24 years ago. On physical examination, a dehydrated, icteric male was seen. There were no enlarged lymph nodes and no pathological findings of heart or lungs. The liver was palpable, 4 cm under the right costal margin.

Laboratory testing revealed a normocytic anaemia (Hb 5.0 mmol/l, MCV 94 fl), thrombocytopenia (platelet count 71 x 10^9/l) and an extreme leucocytosis (white blood cell count 74.7 x 10^9/l; see *table 1* for differentiation). Renal insufficiency was found (serum creatinine 195 µmol/l, serum blood urea nitrogen 22.4 mmol/l) and the liver parameters were abnormal (bilirubin 126 µmol/l (conjugated 86 µmol/l), aspartate aminotransferase 288 U/l, alanine aminotransferase 165 U/l, lactate dehydrogenase (LDH) 1162 U/l, alkaline phosphatase 520 U/l and γ-glutamyltransferase 244 U/l). Prothrombin time and activated partial thromboplastin time were increased (15.1 and 34 seconds, respectively). C-reactive protein (CRP) was elevated (175 mg/l). Because of the extremely high number of mature granulocytes and the absence of immature cells in peripheral blood, a chronic neutrophilic leukaemia (CNL) was suspected. However, the patient refused further diagnostic procedures and succumbed within 24 hours of admission.

At autopsy, an enlarged liver was found with an angiosarcoma showing diffuse growth in the right liver lobe. The liver had ruptured and blood was found in the intra-abdominal cavity. Bone marrow showed normal precursor cells with little hypercellularity of the myeloid precursor cells. It was concluded that the extreme leucocytosis with mature granulocytes was a paraneoplastic effect of the angiosarcoma.

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Table 1. *Differentials of peripheral leucocytes (x 10^9/l) in patients A, B and C*

	Patient A	Patient B	Patient C First admission August 2003	Patient C Second admission January 2004
Leucocytes	74.7	92.2	58.7	224.2
Eosinophilic granulocytes	0	0	0	0
Basophilic granulocytes	0	0	0	0
Band neutrophils	6.7	0	2.3	22.4
Segmented neutrophils	65.7	57.2	45.8	107.6
Lymphocytes	0.7	9.2	7.0	17.9
Monocytes	1.5	9.2	1.2	0
Others:	0	17	4	76
• Blasts	0	0	0	36
• Promyelocytes	0	1	2	7
• Myelocytes	0	10	0	18
• Metamyelocytes	0	6	2	16
• Erythroblasts	0	0	0	4

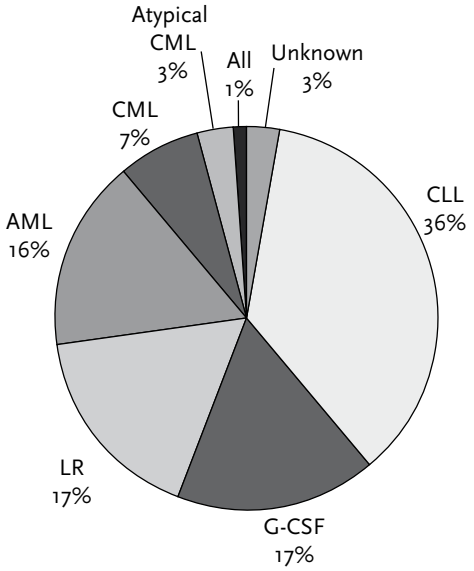
Patient B, an 89-year-old woman, was admitted to the Department of Geriatric Medicine because of severe diarrhoea based on an infection with *Salmonella B*. Her medical history revealed resection of the sigmoid colon due to an adenocarcinoma eight years ago. For a year she had received blood transfusions at regular intervals because she had an anaemia based on myelodysplastic syndrome (MDS) (type refractory anaemia, MDS-RA). During the admission, her condition deteriorated, she developed a severe inflammatory response syndrome (SIRS), and the peripheral leucocyte count increased from 11.8 x 10^9/l at admission to 92.2 x 10^9/l in several days (see *table 1* for differentiation). Laboratory testing revealed a normocytic anaemia (Hb 5.3 mmol/l), increased LDH (2099 U/l) and CRP (175 mg/l). Because an acute leukaemia was suspected, bone marrow aspiration was performed. The bone marrow showed features of MDS-RA with trilineage dysplasia and 1.5% blast cells, so no features of an acute leukaemia. It was concluded that the leucocytosis was caused by the SIRS, probably based on the *Salmonella* infection. The patient was treated with systemic antibiotic therapy and fluid resuscitation. Her condition improved and the leucocyte number decreased to 7.2 x 10^9/l in two weeks. Five weeks after admission she was able to return home.

Patient C, a 77-year-old woman, was admitted to hospital with an abscess of the left anterior tibial muscle. She had undergone coronary artery bypass grafting (CABG) ten years ago. Laboratory testing revealed a microcytic anaemia (Hb 4.9 mmol/l, MCV 72 fl), thrombocytopenia (platelet count 120 x 10^9/l) and leucocytosis (leucocyte count 46.7 x 10^9/l (with 43.0 x 10^9/l mature neutrophilic granulocytes and no immature cells)). CRP was elevated (331 mg/l). Antibiotic treatment was started. After four days, the CRP had decreased (155 mg/l) but the leucocyte count had increased to 58.7 x 10^9/l (see *table 1* for differentiation). Bone marrow aspiration and biopsy showed hypercellular bone marrow with dysplastic features such as micromegakaryocytes, decreased erythropoiesis and dysplastic myelopoiesis. The number of blast cells was not raised (0.5%). After the abscess was drained and the patient recovered, the leucocyte count dropped to 4.4 x 10^9 /l with a normal distribution. Granulocytes still showed hypogranular cytoplasm as a sign of myelodysplasia. It was concluded that she was suffering from MDS-RA and had experienced a leukaemoid reaction associated with a muscle abscess. After four months she was admitted again with a severe anaemia (3.6 mmol/l) and an extreme leucocytosis (214 x 10^9/l; see *table 1* for differentiation). Repeated bone marrow biopsy showed 6% blast cells; therefore it was concluded that there was a progression to refractory anaemia with an excess of blasts (RAEB-t according to FAB classification, RAEB-1 according to WHO classification). Shortly after admission, the patient succumbed.

RESULTS OF RETROSPECTIVE ANALYSIS

We retrospectively investigated the prevalence of an extreme leucocytosis (>50 x 10^9/l) in adult patients in the Meander Medical Centre Amersfoort during a four-year period (January 2000 to December 2003). In this period a white blood cell count >50 x 10^9/l was seen in 147 patients (*figure 1*). As no further information was available for four patients, we were able to analyse data from 143 patients. Ninety-three patients had leukaemia (63%). Twenty-five patients had received subcutaneous injections of G-CSF in order to decrease the leucopenic period after the administration of myelosuppressive chemotherapy (15 patients), or because they were being treated for a haematological malignancy according to a research protocol including the use of G-CSF (ten patients). The leukaemoid

Figure 1. *Causes of extreme leucocytosis (>50 x 10^9/l) in 147 adult patients between 1 January 2000 and 12 December 2003 in the Meander Medical Centre Amersfoort, the Netherlands*



G-CSF = use of granulocyte colony-stimulating factor after chemotherapy; CLL = chronic lymphocytic leukaemia; CML = chronic myeloid leukaemia; AML = acute myeloid leukaemia; LR = leukaemoid reaction.

reaction in the other 25 patients appeared to be associated with other diseases (*table 2*). Nine patients had positive blood cultures for micro-organisms and 11 patients had a malignant disease. Of the remaining patients, one had a biliary pancreatitis, three patients had tissue necrosis due to ischaemia (two enteric, and one leg soft tissue), and one patient had a decompensated cirrhosis. Patient U suffered severe chronic obstructive pulmonary disease and was admitted with a pneumothorax and severe dyspnoea. He died within hours. A possible explanation for the extremely high white blood cell count in this patient could be a combination of severe stress and pneumonia. In both patients with cirrhosis (Patients N and W), the cirrhosis was caused by alcohol abuse. At the time of this investigation (January 2004) only seven of 25 patients were alive (mortality 72%). Ten patients died within two weeks of the leukaemoid reaction.

DISCUSSION

In the three patients described, leukaemia was considered to be a possible cause of the extreme leucocytosis. Based on bone marrow biopsies, however, a leukaemoid reaction

Table 2. *Patients with a leukemoid reaction without use of G-CSF*

Code	Sex	Age	Leucocytes (x 10^9/l)	Died	Malignancy	Infection	Blood culture	Other
A	M	74	74.7	+	Angiosarcoma			
B	F	89	56.5	+	MDS	+		
C	F	77	58.7	+	MDS	+		
D	M	69	65.3	+	Bladder (m)			
E	F	83	63.3	+	Thyroid (m)			
F	F	34	62.9	+				Enteric ischaemia
G	F	65	62.5	+		+	*Pneumococcus*	
H	F	52	61.0	-		+		Biliairy pancreatitis
I	F	68	59.8	+	Sigmoid	+	*Pseudomonas*	
J	F	47	58.9	+	Lung (m)			
K	F	53	56.8	+	Lung (m)	+		
L	F	53	56.4	-		+	*Pseudomonas*	
M	F	93	55.5	+				Leg necrosis
N	F	37	54.9	-				Cirrhosis
O	F	84	53.6	+	Bladder			
P	F	67	52.9	+		+	*Streptococcus A*	
Q	M	35	52.5	-		+	*Streptococcus A*	
R	M	50	52.0	+		+	*Pseudomonas & E. coli*	
S	M	53	51.7	-		+	*Pseudomonas & Streptococcus A*	
T	M	69	51.6	+	Lung			
U	M	78	51.3	+				
V	F	66	50.6	-		+	*E. coli*	
W	M	68	50.2	+		+	*Pneumococcus*	Cirrhosis
X	M	89	50.1	+				Enteric ischaemia
Y	F	74	50.1	-	Lung (m)			

MDS = myelodysplastic syndrome; (m) = metastastic disease.

appeared to be the cause of the peripheral leucocytosis. A leukaemoid reaction is defined as a white blood cell count >50 x 10^9/l with a cause outside the bone marrow.[1] A raised number of white blood cells can be due to mature leucocytes (patient A), resembling a CNL. If an increased amount of immature granulocytes such as (pro)myelocytes or metamyelocytes is seen (Patient B), a leukaemoid reaction can imitate chronic myeloid leukaemia (CML). Investigation of the bone marrow including immunophenotyping may help to differentiate between leukaemia and a leukaemoid reaction. Cytogenetic abnormalities associated with leukaemia should be looked for by karyotyping and by reverse transcriptase-polymerase chain reaction (RT-PCR). The BCR-ABL protein can be found in CML and in some cases in acute lymphoblastic leukaemia or acute myeloid leukaemia. When dysplastic features are found in the bone marrow, the amount of blast cells in the bone marrow should be used to discriminate between a leukaemoid reaction and leukaemia. Because the leucocytosis disappeared upon treatment of the infection in patients B and C, both these patients seemed to have experienced a leukaemoid reaction of a dysplastic bone marrow. In Patient A, the leukaemoid reaction was associated with an angiosarcoma and rupture of the liver.

Not much is known about the incidence and course of leukaemoid reactions. Most knowledge is based on case reports.[2-8] Several known causes of leukaemoid reactions are given in *table 3*. A paraneoplastic leukaemoid reaction can be caused by increased serum levels of G-CSF or other growth factors, which are considered to be produced by the malignant cells, mostly from an endothelial tumour.[3-5] In some reports, a decrease in G-CSF levels was described after treatment of the primary tumour.[6] The leukaemoid reaction can be present even years before the diagnosis of the carcinoma.[7] McKee described a group of 21 patients with a leukaemoid reaction based on a malignant disease of whom 20 suffered a carcinoma, mostly of the lung.[8] In those patients, a leukaemoid reaction was associated with aggressive tumour behaviour and high mortality.[8]

In a retrospective analysis, we identified 50 patients (out of 147 patients with >50 x 10^9/l leucocytes) who met the definition of a leukaemoid reaction. Within this group, 25 of the cases were associated with treatment with G-CSF. In the remaining patients high numbers of malignancies, mainly epithelial, or bacteraemia, were seen, in concordance to earlier reports.

In conclusion, in one third of patients (35%) with an extreme leucocytosis (>50 x 10^9/l), leucocytosis was not caused by leukaemia but by a leukaemoid reaction. This leukaemoid reaction is usually seen in association with a malignancy or a severe sepsis and is characterised by a high mortality.

Table 3. *Several causes of a leukemoid reaction*

Infectious	Shigellosis
	Hepatic abscess
	Tuberculosis
	Sepsis
Paraneoplastic	Bronchus carcinoma
	Carcinoma of bladder, kidney and prostate
	Carcinoma of tongue and nasopharynx
	Carcinoid
	Hepatocellular carcinoma
	Carcinoma of oesophagus
	Cholangiocarcinoma
	Carcinoma of cervix or ovary
	Splenic haemangiosarcoma
	Liposarcoma and soft tissue sarcoma
	Leiomyosarcoma of the bladder
	Melanoma
	Bone metastasis
	Multiple myeloma
	Hodgkin's disease
Drug induced	Granulocyte colony stimulating factor
	Corticosteroids
	Tetracycline
	Streptokinase
Miscellaneous	Diabetic ketoacidosis
	Alcoholic hepatitis
	Ethylene glycol intoxication
	Enteric necrosis

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