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CD4 deficiency in myelodysplastic syndrome with monosomy 7

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Abstract We describe a patient with myelodysplastic syndrome with monosomy 7 presenting with a T-cell defect. He suffered from infections from the age of 10 years, when a CD4 deficiency and impaired lymphoproliferative responses in vitro were found. The only symptom of a myelodysplastic syndrome at that time was thrombocytopenia with giant platelets. Monosomy 7 was found in the bone marrow cells. At the age of 11 years he developed other characteristics of monosomy 7 including splenomegaly and anaemia. Some months later leukaemia was diagnosed.

Conclusion In non-HIV CD4 deficiency myelodysplastic syndrome has to be considered.

Key words CD4 deficiency · Myelodysplastic syndrome · Monosomy 7 · Immunodeficiency

Abbreviations FCM flow cytometric analysis · MDS myelodysplastic syndrome

Introduction

Characteristic features in myelodysplastic syndrome (MDS) with monosomy 7 include recurrent infections, hepatosplenomegaly, lymphadenopathy, (refractory) anaemia, thrombocytopenia, leucocytosis and a hypercellular bone marrow with a slight increase in blast cells. Acute myeloid leukaemia is likely to develop as a terminal event [5]. Monosomy 7 does not usually affect lymphoid subpopulations but is restricted to committed progenitor cells with the capacity to differentiate into mature myeloid cells [2]. We report a patient with MDS presenting with a T-cell defect.

Case report

The patient, a boy, suffered from recurrent upper and lower respiratory tract infections (both otitis media and pneumonia) from the age of 10 years. He had once developed a parotitis due to staphylococci and had extended warts.

On admission at the age of 10.5 years he had enormous warts on his feet and fingers. No other abnormalities were noted on physical examination. WBC and haemoglobin were normal (Table 1). Platelets were unusually large and decreased in number (Table 1). Serum immunoglobulins were normal (Table 1). HIV test was negative. Immunophenotyping by flowcytometric analysis (FCM) of peripheral blood T-cells revealed 44% CD3+ cells ($1.60 \times 10^9/l$) of which were only 13% CD4+ cells ($0.46 \times 10^9/l$) and 32% CD8+ cells ($1.14 \times 10^9/l$), resulting in a reversed T4/T8-ratio (0.4).

Proliferative responses to phytohaemagglutinin and pokeweed mitogen were impaired (Table 1). Monosomy 7 could not be demonstrated in the phytohaemagglutinin-stimulated cells.

Table 1 Haematological and immunological studies in the patient (*PHA* phytohaemagglutinin, *PWM* pokeweed mitogen)

	Age in years					
	10			11		
	7/12	9/12	10/12	0	1/12	3/12
<i>Haematological studies</i>						
Hb g/dl	13.1	12.9	12.0	10.6	10.2	7.0
Platelets 10 ⁹ /l	64	153	80	103	59	16
WBC 10 ⁹ /l	8.7	32.5	10.2	32.8	19.6	30.0
Blasts %				12	10	20
Neutrophils %	36	50	23	19	28	22
Precursors %	1	15	2	26	14	14
Lymphocytes %	40	9	55	16	12	21
Monocytes %	23	24	20	27	36	21
Eosinophils %						2
Bone marrow	Myelomonocytic hyperplasia lymphopenia				Unchanged	Unchanged
Blasts %	4	2			6	16
Karyotype	45 XY, -7					
<i>Immunological studies</i>						
CD3+ cells 10 ⁹ /l	1.60			2.88		1.44
CD4+ cells 10 ⁹ /l	0.46			0.61		0.27
CD8+ cells 10 ⁹ /l	1.14			1.44		0.96
CD4/CD8 ratio	0.4			0.4		0.3
Lymphocyte proliferation in vitro (% of controls) to						
PHA	20%					
PWM	25%					
<i>Serum immuno-globulins</i>						
IgG g/l	7.30			5.82		5.36
IgA g/l	0.92			0.68		0.54
IgM g/l	1.30			1.08		0.84
IgD IU/l	12			7		
IgE IU/l	12			6		

Table 2 Immunophenotyping of peripheral blood cells of the patient at the age of 11 years. Peripheral blood was anti-coagulated with EDTA. Cell samples were stained single or double with immunofluorescing FITC- or PE-labelled monoclonal antibodies according to the full blood method. Expression of varying antigens was determined by flow cytometry in a Coulter Epics Elite. Cell

populations were divided in two clusters based on forward and side scatters. Cluster 1 (Gate A) contained a very immature populations of CD13, 33, 34, 36 positive cells. Cluster 2 (Gate B) contained a more mature myeloid population of CD13, 14, 15, 33 positive, CD34 negative cells

Gate A Nucleated cells: 21%				Gate B Nucleated cells: 59%			
CD2	42%	CD13	45%	CD2	8%	CD13	90%
CD3	38%	CD14	11%	CD3	7%	CD14	59%
CD4	8%	CD15	11%			CD15	95%
CD8	19%	CD33	51%			CD33	99%
CD4/CD45RA	4%	CD34	55%			CD34	16%
CD4/CD45RO	3%	CD36	36%			CD36	
CD3/CD57	4%	CD42	20%			CD42	34%
T4/T8-ratio = 0.4							
CD19	3%	CD56	16%	CD19	1%		

Bone marrow study revealed no leukaemia but was compatible with MDS. Monosomy 7 was demonstrated by cytogenetic studies of bone marrow cells.

At the age of 10 years and 9 months the boy again suffered from pneumonia and had to be treated with antibiotics. At that time he had a leukocytosis with some blasts and immature myeloid cells in peripheral blood (Table 1). He recovered rapidly and his white blood cells became normal again. However, within some months splenomegaly developed. At the age of 11 years haematological studies revealed a slight decrease of haemoglobin to 10.6 g/dl, WBC was increased with metamyelocytes 15% and blasts 12%. T-cell markers were comparable to earlier studies: CD3+ cells 38%, CD4+ cells 8% and CD8+ cells 19% as determined by FCM (Table 2). However, the absolute number of CD4+ cells was only marginally decreased according to age (Table 1). Further analysis of this cell population revealed high percentages of CD34, CD33, CD13 and CD36 positive cells (Table 2). These results suggested the presence of an early myeloid progenitor population in the peripheral blood of this patient.

At the age of 11 years and 3 months he became anaemic. CD4 deficiency was again present (Table 1). Bone marrow studies now revealed a high percentage of blast cells (Table 1) raising the suspicion of a developing leukaemia. He was initially treated with cytostatics. Recently a bone marrow transplantation was performed.

Discussion

The clinical symptoms of this patient are similar to those found in immunodeficiency. The laboratory findings of this patient, particularly the decreased number of CD4+ cells attended with the impaired lymphoproliferative stimulation tests are strongly reminiscent of HIV infection as are the unusual verrucous reactions [4]. However, HIV tests remained negative. The boy suffered from MDS with monosomy 7. Recurrent acute infections, often resulting

in significant morbidity and mortality are a prominent feature of MDS [2, 3]. The increased susceptibility to infections in patients with MDS is thought to be due to neutropenia or functional defects of neutrophils. Neutrophil function tests sometimes reveal defective chemotaxis with reduced killing despite a normal nitrozoilium blue test. The clinical symptoms in our patient were those of a T-cell defect and preceded the anaemia and the leukaemic stage of the disease.

Abnormalities in T-lymphocytes, namely an imbalance between both major T-cell subsets and a reduced proliferative response to mitogenic stimulation, have been described in MDS patients [1]. In this study only patients who had either a cytopenia affecting one or more of the peripheral myeloid lines or a peripheral monocytosis were investigated. Most of them had already refractory anaemia and some had developed chronic myelomonocytic leukaemia. The boy presented here with monosomy 7 was investigated in an earlier stage of the disease and did not have a cytopenia. Whether his lymphocyte abnormalities represent a primary defect of the lymphocytes is not clear. In the lymphocytes cultured in vitro with phytohaemagglutinin monosomy 7 has not been demonstrated. At that time not only the CD4 deficiency was present but the platelets were also decreased in number and were of giant size. In the patient presented a T-cell defect was present before the characteristic features of MDS e.g. (refractory) anaemia and hepatosplenomegaly developed. Only the thrombocytopenia pointed to the diagnosis of MDS. We suggest that in non-HIV CD4 deficiency MDS might be causally related to the T-cell defect.

References

1. Bynoe AG, Scott CS, Ford P, Roberts BE (1983) Decreased T helper cells in the myelodysplastic syndromes. *Br J Haematol* 54: 97-102
2. Gerritsen WR, Donahue J, Bauman J, Jhanwar SC, Kernan NA, Castro-Malaspina H, O'Reilly RG, Bourhis JH (1992) Clonal analysis of myelodysplastic syndrome: monosomy 7 is expressed in the myeloid lineage, but not in lymphoid lineage as detected by fluorescent in situ hybridization. *Blood* 80: 217-224
3. Koeffler HP, Golde DW (1980) Human preleukaemia. *Ann Int Med* 93: 347-353
4. LeBoit PE (1992) Dermatopathologic findings in patients infected with HIV. *Dermatol Clin* 10: 59-71
5. Sieff CA, Chessells JM, Harvey AM, Pickthall VJ, Lawler SD (1981) Monosomy 7 in childhood: a myeloproliferative disorder. *Br J Haematol* 49: 235-249