

## CASE REPORT

### Polychondritis Terminating in Eosinophilic Leukemia

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We report here on a patient presenting with Relapsing Polychondritis (RP) two years before the diagnosis of Myelodysplasia (MDS) terminating in Eosinophilic Leukemia (EoL). The evolution of RP several years prior to the presentation of MDS does not support a paraneoplastic etiology of RP in this patient. The terminal development of EoL in our case is assumed to represent clonal evolution

caused by a second mutagenic event. The existence of autoimmune skin disorders in both the patient and his offspring (vitiligo and subacute cutaneous lupus erythematosus, respectively) implies that the coexistence of MDS and RP may have been caused by a functional disturbance of the immune system. (Pathology Oncology Research Vol 3, No 2, 135–138, 1997)

**Keywords:** relapsing polychondritis, vitiligo, myelodysplasia, eosinophilia, eosinophil leukemia

#### Introduction

There is a well documented relationship between myelodysplasia (MDS) and autoimmune disorders,<sup>1</sup> such as relapsing polychondritis (RP), which is a rare autoimmune disease.<sup>2</sup> Despite evidence of the involvement of the immune system in myelodysplasia, the exact pathogenetic mechanism is still unknown.<sup>3,4</sup> Blastic transformation of MDS leading to overt leukemia is an ominous feature of this condition. This report may contribute to a better understanding of the underlying processes involving the immune system and hematopoiesis in MDS.

#### Case report

The patient was a 69-year old male who first presented with a painful swelling and redness of his left ear in October 1991. In February 1992 there was spontaneous discharge from his left ear. His blood cell counts were normal at the time (*Table 1*). In the same year the inflammation of his left ear recurred twice and subsided without antibiotic therapy. In April 1995 an inflammation of the

right auricle was seen. Both anemia and thrombocytopenia were detected at that time. Two months later the right auricle became inflamed and thickened without involvement of the adjacent skin. The patient was febrile. At the same time the tip of the nose became red and the left ear seemed to have lost its firm structure as a result of the previous inflammation. The hematological parameters showed further decline. On the first clinical admission in September 1995 he was pale and vitiligo was seen on the chin, the forearms and trunk. The right ear and the tip of the nose were inflamed, the cartilage of the right ear was thickened. Interestingly, his daughter had subacute cutaneous lupus erythematosus. The patient was a heavy drinker and smoker employed as a petrol station worker for 6 years. He developed severe hearing impairment in the last few years. On admission, anemia and thrombocytopenia were found (*see Table 1*). The differential count showed 10% immature blastic elements, 4% mature eosinophils, 2% basophils and 18% normoblasts, giant thrombocytes and pseudo-Pelger anomaly. On cytochemical evaluation a myelomonocyte character of the blasts could be demonstrated. On iliac crest bone biopsy myelodysplastic changes were found characteristic of RAEB (refractory anemia with excess blasts) according to the FAB classification. The ear roentgenogram revealed pathological alteration in the structure of the left ear (*Fig. 1*). Biopsy specimen of the right ear showed destruc-

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**Table 1. A summary of hematological parameters**

Time (month/year)	WBC ( $\times 10^9$ /l)	PCV (%)	Hb (g/dl)	PLT ( $\times 10^9$ /l)	Absolute eosinophil cell count
February/1992	5.6	nd	15.5	ND	ND
September/1992	5.4	48	12.4	ND	ND
April/1992	4.9	27	9.2	88	ND
Júly/1992	4.2	19	7.1	45	ND
September/1995	7.5	25	6.5	56	300
October/1995	10.1	20	7.3	45	2000
November/1995	13.8	20	4.7	41	5520

tion of the cartilage (Fig.2.). Using Alcian blue, PAS staining acidic or neutral polysaccharide materials were not found in the cartilage.

On ophtalmological examination there were no signs of RP other than a slight thinning of the edge of the cornea.

The patient was given a low-dose treatment of Alexan (20 mg /day) along with Prednisolone (25 mg/day). In October 1995 marked anemia, leukocytosis, and thrombocytopenia were found. The differential count revealed 12% of blasts and 20% of eosinophil band and segmented forms. The patient was given a blood transfusion. In November 1995 septicemia occurred with fever. The differential count was 3% blasts, 40% eosinophil band and segmented forms and 16% normoblasts along with giant thrombocytes. No alterations could be seen on 2D echocardiography. In addition to the previously detected mild hepatosplenomegaly, enlarged lymph nodes in the hepatic and splenic hilar region as well as retroperitoneally were detected by abdominal ultrasonography.

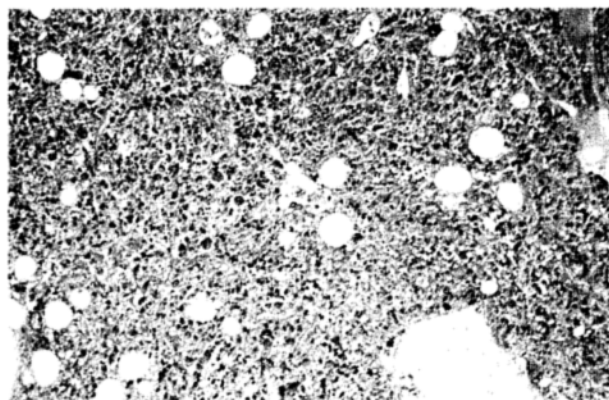
Trephine biopsy showed marked eosinophilia without any sign of progression to blastic transformation. At two



**Figure 1.** Ear roentgenogram showing the patient's left and right ears. Note the distorted structure.

weeks into his hospitalization, pulmonary infiltration was visible on chest X-ray. Despite the antibiotic and supportive therapy, cardiorespiratory insufficiency developed and the patient died on 30th November 1995.

At autopsy pneumonia was found as cause of death. Expansion of the bone marrow was also demonstrated. On microscopic evaluation the bone marrow, the liver and the abdominal lymph nodes were found to be infiltrated 80% with immature eosinophils that was consistent with EoL (Fig. 3). The eosinophils showed resistance on KCN-POX cytochemical staining procedure. Cartilaginous tissues other than the ear or nose were intact.

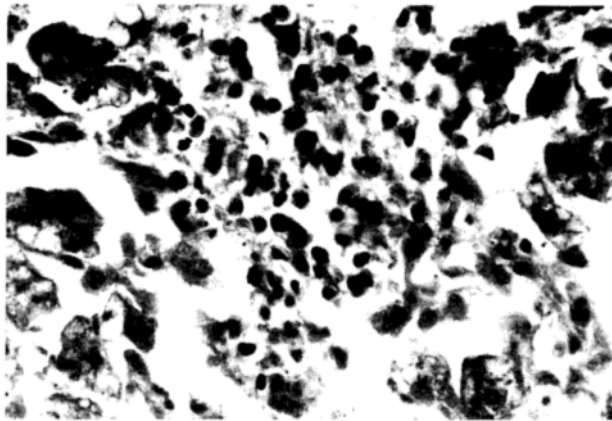


**Figure 2.** The original structure of the ear cartilage is distorted. Chondrocytes diminished in size, invaded by segmented leukocytes, macrophages, lymphocytes and plasma cells causing irregular fragmentation of the border zone. Adjacent to the damaged part of the cartilage eosinophils appeared in large amounts. Focal calcification is present. Original magnification:  $\times 150$ .

## Discussion

Relapsing polychondritis is an autoimmune disorder characterised by a decrease in the proteoglycan content of the cartilaginous tissues accompanied by lacunar-type death of the chondrocytes. According to recent investigations, immunologic processes may participate in the pathogenesis of the disease. Immunoglobulin and complement component deposition may occur in the inflamed tissues. Immune complexes or autoantibodies to type II collagen may be demonstrated in some cases.<sup>5</sup> There are observations confirming the assumption that cellular response may play a role in the pathogenesis.<sup>6</sup> RP is a rare disease with periodic manifestation of symptoms and generally with progressive inflammation of cartilaginous structures throughout the body. Diagnostic criteria and characteristic histology have been described in several reports.<sup>7,8</sup>

Immune abnormalities in myelodysplastic syndromes are well known.<sup>3,4</sup> Castro et al found that the rate of occurrence of autoimmune disorders is 10% in patients



**Figure 3.** Biopsy from the lymph node showing rough granulation in the infiltrating eosinophils with irregular nuclei.

with MDS. These include vasculitis, joint inflammation and neuropathies. RP rarely occurs in combination with MDS (Table 2). There are case reports in the literature describing RP developing after or simultaneously with MDS.<sup>2,9,10</sup> In our case RP preceded the clinical manifestations of MDS. The prognosis of MDS in association with RP is poor.<sup>11</sup> According to previous publications, eosinophilia may occur in association with MDS<sup>12</sup> and there were some cases in which acute EoL developed after MDS.<sup>13,14</sup>

In the case reported by Pérez-Losada, eosinophilia was present until the patient with RA developed acute leukemia. The latter was consistent with the reactive phenotype of eosinophilia; however, a malignant behaviour of eosinophils could not be demonstrated on culture studies and these cells had a normal chromosome karyotype as well.

There are also observations regarding cancer-associated eosinophilia, e.g. eosinophilopoietic activity of tumor-extracts on normal stem cell colonies. Yano et al had similar findings in a patient with adult T cell leukemia.<sup>15</sup> The serum of our patient did not significantly induce more

eosinophil colonies (CFU-EO) than sera collected from normal individuals on normal bone marrow stem cells in a colonisation assay.<sup>16,17</sup> This may indicate that in EoL the leukemic clone produces eosinophils without external stimulus whereas in other tumors, eosinophilia is a paraneoplastic phenomenon. This may be supported by the observation that eosinophilic colonies of PBMC (peripheral blood mononuclear cells) derived from an EoL patient were formed spontaneously in clonal assay without rhGM-CSF.<sup>13</sup>

Inversion of chromosome 16 and cytogenetic abnormalities involving chromosome 5 are frequently associated with idiopathic hypereosinophilia or EoL.<sup>18</sup> Genes encoding for cytokines with eosinopoietic activity such as IL-3 and IL-5 reside on the long arm of chromosome 5. Although in our case a chromosomal analysis has not been performed, a second mutagenic event is suspected to be responsible for the transformation of MDS into EoL as suggested by the finding of Murakawa et al.<sup>13</sup>

The diagnosis of EoL in our case was confirmed by autopsy according to the criteria of EoL.<sup>19</sup> The bone marrow and other organs (liver, lymph nodes) were infiltrated with immature eosinophilic cells.

Several questions arise in relation to our case: Is the unknown initiating factor of RP responsible for MDS, or rather, may their coexistence be caused by a functional disturbance of the immune system? The presence of multiple autoimmune disorders in our patient's family may support such a mechanism. Finally, could the patient's chronic exposure to benzole be responsible for the development of both the MDS and RP?

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**Table 2.** Reported cases of MDS associated with RP (data obtained from the literature)

Author	Year	Age (years)	Sex	Clinical manifestation of MDS	Therapy	Length of survival (months)
Arlet et al.	1989	71	m	RAEB	NA	120
Arlet et al.	1989	56	m	RAEB	NA	6
Van Besien et al	1992	19	m	RAEB-t	P	ND
Shirota et al	1993	63	f	RA	P,AC	3
Diebold et al	1995	66	m	MDS	C	55
Diebold et al	1995	64	m	MDS	C,A	44
Diebold et al	1995	63	m	MDS	C,CP	10

C – corticosteroid, A – azathioprine, CP – cyclophosphamide, AC – ara-c, P – prednisone, NA – no data, RAEB – refractory anaemia with excess blasts, RA – refractory anaemia, MDS – myelodysplastic syndrome

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