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Central nervous system involvement in acute promyelocytic leukemia. A description of two cases and review of the literature

Sir,

Extramedullary involvement is infrequent in acute promyelocytic leukemia (APL), but it has been suggested that its incidence might be increasing. Two patients with APL and central nervous system (CNS) involvement are described and the possible relationship between this complication and new treatment approaches of APL are discussed.

Case #1. A 45-year-old woman was diagnosed with APL. Cytogenetic studies revealed a complex karyotype in bone marrow (46,XX,r(9) t(17;15;10) (q11; q22;q24) and a bcr-1 pattern of the PML-RARα fusion protein. A molecular complete remission (CR) was achieved within the first month from starting ATRA and standard chemotherapy. Five days after administration of a consolidation course she presented with a third cranial nerve palsy and examination of the cerebrospinal fluid revealed the presence of promyelocytes in which the PML-RARα rearrangement was detected. She was given ATRA plus intrathecal chemotherapy without achieving a response and died shortly thereafter from progressive disease.

Case #2. A 45-year-old man was diagnosed with APL and a bcr-1 pattern of the PML-RARα fusion protein was demonstrated in peripheral blood. CR was achieved after treatment with ATRA and standard chemotherapy. Twenty months later he presented with a bone marrow relapse. After attaining a second CR he underwent an allogeneic bone marrow transplantation (BMT). Twenty months after the BMT he developed a spinal cord syndrome due to a paravertebral mass. Biopsy of the tumor revealed promyelocytes with a PML-RARα rearrangement (bcr-1). Despite treatment with ATRA and local radiotherapy, the patient died from disease progression.

Extramedullary involvement, including CNS infiltration, has been rarely reported in APL. It usually occurs

Table 1. Reported cases of extramedullary disease in APL.

Author	*Year*	*A/S*	*ATRA**	*Extramedullary site*	*Interval*	*Cyto*	*Outcome*
Bermengo	1975	82/M	No	Cutaneous	0m	NA	Death (PD)
Belasco	1978	9m/M	No	Soft tissue	0m	NA	CR
Nihei	1984	55/M	No	Mediastinum and muscle	4m	NA	Death (PD)
Kubonishi	1984	23/M	No	Mediastinum	0m	NA	Death (PD)
Kanakura	1987	44/F	No	Intracerebral mass, CSF	0m	NA	CR (23m)
Baer	1989	59/F	No	Cutaneous	36m	NA	BM relapse
Zuiable	1989	31/M	No	SNC (extradural mass)	0m	No	BM relapse
Rush	1990	13m/M	No	Mandibular	22m	No	CR (16m)
Ajarim	1990	21/M	No	Mediastinum (also BM)	0m	No	BM relapse
Niazi	1991	26/M	No	Cutaneous and CNS	NA	NA	Death (PD)
Brown	1992	37/F	No	Optic nerve (also BM)	22m	Yes	CR (NA)
Longacre	1993	19/M	NA	Cutaneous	NA	NA	NA
Thomas	1994	68/F	Yes	Subcutaneous	10m	Yes	CR (8m)
Weiss	1994	31/M	Yes	External auditory canal	11m	Yes	CR (NA)
Weiss	1994	33/M	Yes	Cutaneous &lymph node	11m	Yes	CR (NA)
Giralt	1994	23/M	Yes	Cutaneous & CSF	13m	Yes	CR (NA)
Giralt	1994	35/M	Yes	Cutaneous	1,5m	Yes	Death (PD)
Giralt	1994	47/F	Yes	Cutaneous	5m	NA	Death (PD)
Tosi	1995	27/M	No	Epidural	0m	Yes	CR (14m)
Hazneradoglu	1995	19/M	No	Gingiva	15m	NA	Death (PD)
Békássy	1995	24/F	NA	Cutaneous	NA	NA	Response
Békássy	1995	3/F	NA	Spinal	NA	NA	Death (PD)
Békássy	1995	26/M	NA	Testicle&spinal	NA	NA	Death (toxic)
Lederman	1995	46/F	No	Subcutaneous&CNS	6m	Yes	Response
Selleri	1996	31/F	No	Cutaneous	18m	Yes	CR (25m)
Wiernik	1996	5/F	Yes	Gingiva	21m	Yes	Death (PD)
Wiernik	1996	25/F	No	Cutaneous (also BM)	6m	Yes	Death (PD)
Chen	1996	74/M	No	Spleen	0m	Yes	Death (PD)
Martinelli	1997	42/M	No	Bone (L4)	0m	Yes	BM relapse
Evans	1997	23/M	Yes	CNS	15m	Yes	Death (GVHD)
Evans	1997	22/M	Yes	Bone (mastoid)	6m	Yes	CR (NA)
Evans	1997	49/F	Yes	CNS(CSF+)	NA	Yes	Death (PD)
Molero	1997	40/M	Yes	CNS(CSF+)	13m	Yes	Death (PD)
Ueda	1997	66/M	Yes	Cutaneous (also BM)	7m	Yes	NA
Del Río	1997	28/F	No	Cutaneous (also BM)	7m	NA	PD
Kishimoto	1997	11/F	Yes	Cutaneous	2-3m	Yes	PD
Castagnola	1997	23/M	No	CNS	11m	Yes	Death (PD)
Maloisel	1997	42/M	Yes	Colon	NA	Yes	Death(PD)
Forrest	1997	34/M	Yes	Testicle	120m	Yes	Death (PD)
Liso	1998	17/M	No	Lymph node	25m	Yes	Death (PD)
Liso	1998	48/M	No	Cutaneous	14m	Yes	Death (PD)
Liso	1998	22/F	No	Cutaneous	14m	Yes	Death (GVHD)
Liso	1998	25/F	No	Cutaneous	12m	Yes	Death (PD)
Liso	1998	30/M	Yes	CNS (CSF+)	9m	Yes	CR (12m)
Liso	1998	44/F	Yes	Cutaneous	10m	Yes	CR (20m)
Liso	1998	45/M	Yes	Cutaneous	0m	Yes	CR (31m)
Present case		37/F	Yes	CNS (CSF+)	1,5m	Yes	Death (PD)
Present case		45/M	Yes	CNS (extradural mass)	31m	Yes	Death (PD)

A/S: age and sex; ATRA: prior therapy with ATRA; Interval: months from diagnosis to extramedullary disease; Cyto: t(15;17)/PML-RARα fusion protein. BM: bone marrow; CSF: cerebrospinal fluid; PD: progressive disease; NA: not available.

shortly before or concomitantly to a bone marrow relapse, although in some cases it is apparent at the diagnosis or late in the course of the disease, up to ten years from the initial diagnosis. The skin or the CNS are the sites most frequently involved. Although the prognostic significance of extramedullary involvement in APL has not been formally assessed, from a review of the literature (see Table 1), it appears that about one third of patients may achieve a complete and in some cases sustained remission of the disease. Whether the incidence of this complication is increasing is a matter of debate, as it is its potential relationship with ATRA therapy.[1-4] A number of reasons could account for the increased incidence of extramedullary involvement. Firstly, the longer survival of patients treated with ATRA would increase the number of patients at risk of developing this type of relapse. Secondly, *in vitro* studies have shown that ATRA modulates the expression of adhesion molecules in APL cells enhancing their adhesiveness and motility.[5,6] These mechanisms might explain the efflux of leukemic cells from the bone marrow to the tissues in the ATRA syndrome and might also play a role in extramedullary relapses after ATRA treatment. Nevertheless, extramedullary APL may develop after chemotherapy or at presentation. In conclusion, although rare, extramedullary involvement is possible in patients with APL, a fact that should be considered in the management of these patients. Finally, the actual incidence of this complication and its relationship to new therapies should be prospectively assessed.[7-10]

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Key words

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Legionella sp pneumonia in patients with hematologic diseases. A study of 10 episodes from a series of 67 cases of pneumonia

Sir,

Legionella pneumophila is a significant pathogen for immunocompromised patients, especially for those with impaired cell-mediated immunity.[1,2] In spite of the fact that patients with malignant hematologic diseases frequently have neutropenia and/or immunosuppression and usually receive glucocorticoids as cytotoxic drugs, information about the prevalence and evolution of pneumonias by *Legionella sp* in these patients is scarce.[2] We summarize the presenting features and response to treatment of 9 patients with hematologic diseases who developed 10 episodes of *Legionella* pneumonia diagnosed in a single institution over a 2.5-year period.

A study of all cases of pneumonia diagnosed in a hematology unit from January 1995 to June 1998 was carried out. One hundred and twenty-seven episodes of pneumonia in 106 patients were diagnosed, 68 were community-acquired and 59 nosocomial. In 67 cases radioimmunoassay for *Legionella pneumophila* serogroup 1 (LPS1) antigen in urine was performed, being positive in 10 (one patient had two episodes of pneumonia). In two cases, *Legionella* was also identified in the culture of bronchoalveolar lavage (performed in 15 cases of pneumonia). In the present study, *Legionella pneumophila* was the most frequently found micro-organism (10 cases, 15%), followed by *Streptococcus pneumoniae* (9 cases, 13%) and *Pseudo-*