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Histopathological and Immunohistochemical Studies of Polymorphic Reticulosis

Young Nyun Park, Woo Ick Yang, Kwang Gil Lee and In Joon Choi

This study reviewed 65 cases of polymorphic reticulosis (PR) with respect to clinical and histopathologic bases, and immunohistochemical studies were done using MT1 and UCHL as T-cell markers, MB2 as a B-cell marker and alpha-1-antichymotrypsin as a histiocytic marker. The results obtained were as follows: 1. The male to female ratio was 2.4: 1 and the mean age of patients was 44.5years. The sites involved primarily were the nasal cavity, tonsil and pharynx and about one-fourth of the total cases showed extensive involvement of two anatomical sites at initial presentation. 2. Almost all cases showed characteristic histologic features similar to those of peripheral T-cell lymphoma and showed positive reaction to the T-cell marker. The above immunohistochemical findings suggest strongly that quite a significant portion of PR is in fact T-cell lymphoma.

Key Words: Lethal midline granuloma, polymorphic reticulosis, peripheral T-cell lymphoma

Destructive and ulcerative lesions of the upper aerodigestive tract are frequent but in the pathologic aspect, diagnostic difficulties are occasionally encountered due to the small size of biopsied tissue and associated infiltration of inflammatory cells and necrosis (Kim *et al.* 1978; Cho *et al.* 1983).

So-called lethal midline granuloma (LMG) represents a disease category characterized by a progressive unrelenting ulcerodestructive lesion of the nasal cavity and the midline facial tissue. This particular type of disease is heterogeneous in its pathogenesis. Therefore, a confirmative pathologic diagnosis of biopsied tissue is important for the correct treatment (Resnick and Skerrett 1959; Everette 1965; Kassel *et al.* 1969; Birt 1970; DeRemee and McDonald 1976; Fauci *et al.* 1976; Nelson 1984; Costa and Delacretaz 1986). LMG consists of three different groups by recent classification (Fu *et al.* 1988); Wegener's granulomatosis (McDonald *et al.* 1974; Mcdonald *et al.* 1981; Gross *et al.* 1986), polymorphic reticulosis (PR) (Fechner and Lamppin 1972; Mcdonald *et al.* 1976) and idiopathic midline destructive disease (Kornblut and Fauci 1982; Tsokos *et al.* 1982).

PR had been considered as inflammatory lesion (Friedman *et al.* 1978) or hypersensitivity reaction like Wegener's granulomatosis (Blatt *et al.* 1959), but further clinicopathologic and immunohistochemical studies recently suggested that PR is a neoplastic proliferation of T-cell lymphocytes, similar to lymphomatoid granulomatosis (Katzenstein *et al.* 1979; Stamenkovic *et al.* 1981; Sordillo *et al.* 1982; Jaffe 1985; Gaulard *et al.* 1988). It is said that the characteristic loss of one or more pan T antigens in PR supports that PR is one of the peripheral T-cell lymphomas (PTL), because it has not been observed in the non-neoplastic, normal and reactive lymphoid processes but can be found in PTL (Yoshifumi *et al.* 1982; Weiss *et al.* 1985; Lippman *et al.* 1987; Chott *et al.* 1988). There are, however, some controversies about its real nature. Some investigators, after immunogenetic analysis of PR on the immunoglobulin and T-cell receptor beta-chain gene, proposed that PR is a malignant lymphoma of B-cell lineage (Lin *et al.* 1989), and some authors reported that the malignant lymphoma developed in Waldeyer's ring other than the nasopharynx is of B-cell origin (Noboru *et al.* 1985; Chan and Ng 1987).

Moreover, the reports about the prognosis of PR show some diversities in the results obtained by local

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Address reprint requests to Dr. I J Choi, Department of Pathology, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul, Korea, 120-752

radiation (Cho *et al.* 1986) and in the progression after irradiation (Kim *et al.* 1984).

We performed clinical, histologic and immunohistochemical studies to determine whether PR is one of the malignant lymphomas or a unique entity and to identify the origin of the atypical proliferating cells.

MATERIALS AND METHODS

Sixty-five cases reported as PR or malignant lymphoma were selected from the cases submitted to the Department of Pathology, Yonsei University College of Medicine under the clinical impression of LMG from January 1979 to December 1988.

Serial biopsies were available in 43 cases and the total number of specimens obtained was 91.

All tissue was fixed in 10% buffered formalin and sections were stained by the H-E method. Immunohistochemical studies were performed in 41 cases utilizing UCHL. MT1, MB2 and alpha-1-antichymotrypsin as primary antibodies. The immunohistochemical method used was the ABC method utilizing the Vector Elite-ABC kit (Vectastain Elite ABC kit, Vector Lab, U.S.A.)

The clinical records of patients were reviewed for age, sex, sites of lesion, number of biopsies and serum level of erythrocyte sedimentation rate (ESR).

RESULTS

Clinical Features

The cases subjected in this study were 46 men and 19 women, giving a male to female ratio of 2.4: 1. The age of the patients ranged from 15 years to 83 years with a mean of 44.5years (Table 1).

The site of the lesion was summarized in Table 2.

Table 1. Age incidence

Age (yrs) range	No. of cases
11 - 20	7
21 - 30	10
31 - 40	12
41 - 50	9
51 - 60	16
61 - 70	4
71 - 80	6
81 - 90	1

The most common site was the nasal cavity and about one-fourth of the cases showed extensive involvement of two anatomical sites at initial presentation. Seven cases demonstrated cervical lymphadenopathy.

The number of biopsies done in the same patient until a confirmative diagnosis was made ranged from 1 to 5 with a mean of 1.4 (Table 3).

The levels of serum ESR, checked in 18 cases, were above normal limit ranging from 13 mm/hr to 53 mm/hr with a mean of 32.2mm/hr. The cases with severe necrosis and heavy infiltration of inflammatory cells revealed a higher level but there was no relation between serum ESR level and the cell type of PR.

Histopathologic Findings

Although, in general, the specimens obtained from the patients showed extensive necrosis, a viable portion of the tissue was noted. The viable portion demonstrated diffuse infiltration of atypical cells of small to large size with irregularly distorted hyperchromatic nuclei and angiocentricity, angioinvasion and epitheliotropism which are characteristically observed in PTL. Granulation tissue, fibrosis and inflammatory cell infiltration consisting of granulocytes, macrophages and plasma cells were present around

Table 2. Sites of lesion

Site	No. of cases
Nasal cavity	25
Oral cavity	4
Palatine tonsil	15
Pharynx	3
Larynx	2
Nasal cavity & pharynx	12
Nasal cavity & larynx	1
Nasal cavity & palatine tonsil	1
Palatine tonsil & pharynx	1
Palatine tonsil & larynx	1

Table 3. Number of biospies done before a confirmative diagnosis

No. of biopsies	No. of cases
1	48
2	12
3	2
4	2
5	1

Table 4. Histologic characteristics

Diffuse growth pattern
Angiocentricity and angioinvasion
Epitheliotropism
Ischemic necrosis
Pleomorphism
Weirdly distorted nuclei
Admixture with reactive elements

Table 5. Classification by Japanese lymphoma study group

Grade	Cell Type	No. of cases (%)
Low	Pleomorphic small	37 (56.9)
High	Pleomorphic medium & large	27 (41.5)
	Immunoblastic	1 (1.6)

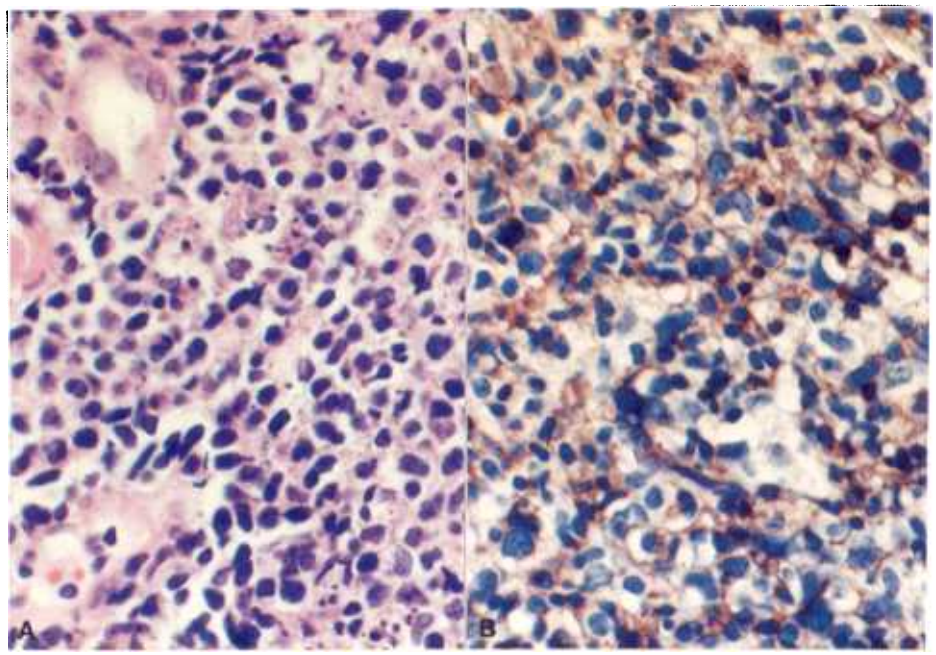

Fig. 1. *Pleomorphic small cell type. a) Diffuse proliferation of atypical pleomorphic small lymphocytes (H & E, ×400). b) Positive cytoplasmic stain for MT1 (PAP, ×400).*

the necrotic areas. These histologic findings were demonstrated in almost all cases examined (Table 4).

Subclassifying PR according to the classification of a Japanese lymphoma study group (Suchi *et al.* 1987), the low grade, pleomorphic small cell type (PSC) was most common (37 cases, 56.9%), fc'lowed by the high grade, pleomorphic medium and large cell type (PMLC) (27 cases, 41.5%) and immunoblastic type (1 case, 1.5%) (Table 5). PSC revealed diffuse proliferation of atypical, pleomorphic small lymphocytes (Fig. 1). The PMLC showed sheet-like growth of atypical cells of medium and large size (Fig. 2). The immunoblastic type displayed diffuse proliferation of relatively uniform large cells with prominent nucleoli and relatively vesicular chromatin (Fig. 3). There was a tendency to diagnose PSC as PR and PMLC as malignant lymphoma, reviewing the previous pathologic reports ($p<0.05$).

The cases were divided into mild, moderate and severe, according to the degree of inflammatory cell infiltration (Table 6). PMLC showed a lesser degree of inflammatory cell infiltration than PSC ($p<0.05$).

Results of Immunohistochemical Study

The results of immunohistochemical study are tabulated in Table 7. Most of the cases (92.7%) showed positive reaction to T-cell marker. Two cases that developed in the palatine tonsil and the base of the tongue showed positive reaction to B-cell marker. No

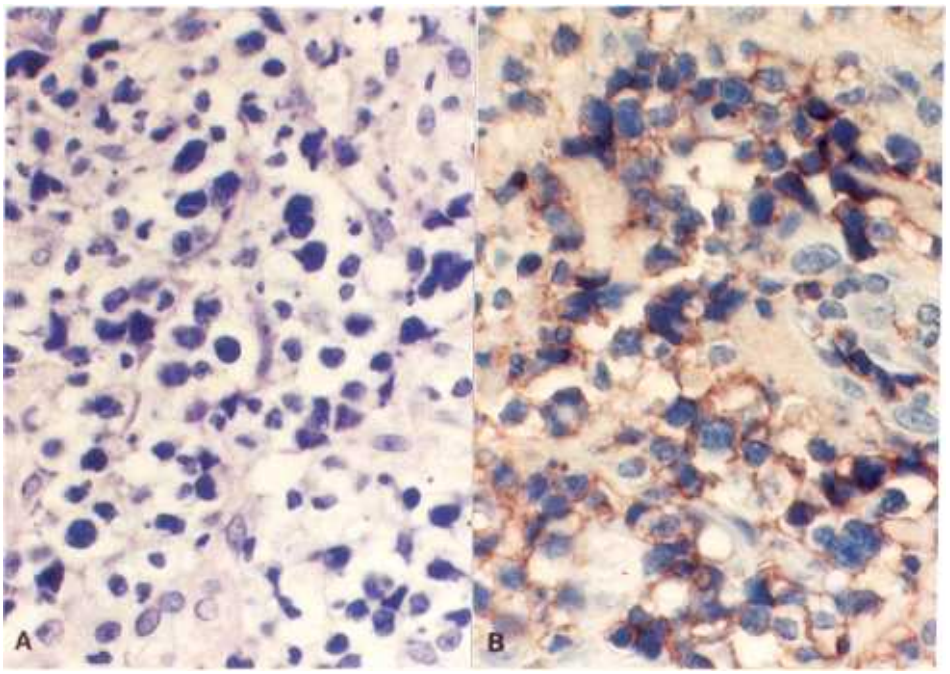

Fig. 2. PLeomorphic medium and large cell type. a) Sheet-like growth of large atypical lymphocytes with clear cytoplasm (H & E, ×400). b) Positive reaction for MT1 (PAP, ×100)

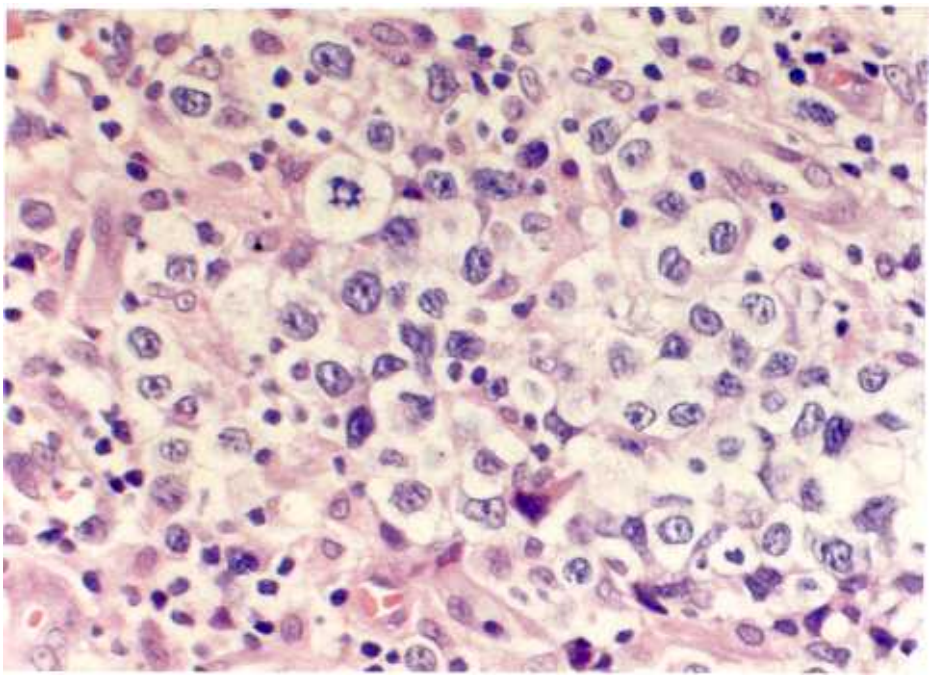

Fig. 3. Immunoblastic cell type. Diffuse proliferation of relatively uniform sized atypical lymphocytes with prominent nucleolus (H & E, ×400).

Table 6. Classification by degree of reactive elements

Cell type	Degree of reactive elements		
	I	II	III
Pleomorphic small	4	28	5
Pleomorphic medium & large	23	4	0
Immunoblastic	1	0	0

Table 7. Results of immunohistochemical study (n=41)

MT1	UCHL	MB2	AACT	No. of cases (%)
+	−	−	−	3 (7.3)
−	+	−	−	0 (0.0)
+	+	−	−	35 (85.4)
−	−	+	−	2 (4.9)
−	−	−	+	0 (0.0)
−	−	−	−	1 (2.4)

AACT: alpha 1-antichymotrypsin

case showed positive reaction to histiocyte marker. One case, of immunoblastic type, showed negative reaction to all the cell markers.

Prognosis

According to the patients' medical records, 6 cases expired within 6 months after the diagnosis; 2 cases PSC, 3 cases PMLC, and one case immunoblastic type. Two cases, expired between 6 and 12 months, were all PSC, low grade.

DISCUSSION

Clinical features such as age, sex and sites of involvement were not different from those of the previous reports of PR. The elevated level of serum ESR is helpful for the diagnosis of PR and the serum ESR levels were over 60mm/hr in 90% of the patients with PR (McClatchey *et al.* 1987). The levels of serum ESR, checked in 18 cases, before corticosteroid treatment, were all increased above normal limit and ranged from 13 mm/hr to 53 mm/hr with a mean of 32.2 mm/hr. The administration of antibiotics before checking ESR probably decreased the level of serum ESR. The diagnosis of PR is occasionally difficult to make due to the small size of biopsied tissue, infiltration of inflammatory cells and necrosis, requiring frequent rebiopsies of more than two times (Kim *et al.* 1978). In this study, the mean number of biopsies was 1.4 which was lower than expected. Obtaining multiple chips of a deeper portion at the initial biopsy probably reduced the total number of biopsies.

Some consider PR as a unique entity, and polymorphism and chronic inflammatory cell infiltration in and around the tumor may help to distinguish PR from malignant lymphoma (Fechner and Lamppin, 1972). Jaffe (1985) introduced the unifying concept of "angiocentric immunoproliferative lesion" to encompass a spectrum of disorders ranging from benign lymphocytic vasculitis to LG/PR and angiocentric lymphoma. Characteristically, all cases of this study showed a diffuse growth pattern, angiocentricity. angioinvasion, epitheliotrophism, weirdly distorted nuclei and admixture with reactive elements and these histologic features are very similar to those of PTL. PMLC showed an inclination to have a lesser degree of inflammatory cell infiltration than PSC and the tumor cells revealed a sheet-like growth pattern. This may cause a tendency to diagnose PSC as PR and PMLC as malignant lymphoma. For the angiocentricity and angioinvasion, an intensive inspection of adjacent areas to the blood vessel may be useful to identify atypical cells as a clue to diagnosis. The variation of ischemic necrosis and inflammatory cell infiltration observed in biopsies of the same patient may be influenced by the biopsy site of the lesion, the state to which the disease has progressed and administration of antibiotics.

At present PR is considered to be a neoplastic proliferation of lymphocytes. Some authors (Yoshihumi *et al.* 1982; Jaffe 1985; Chan *et al.* 1987; Lippman *et al.* 1987) suggest that the origin of atypical lymphocytes is T-cell and the characteristic loss of one or more pan T-cell antigens strongly supports the evidence of PR as one of the PTL (Chott *et al.* 1988). However, Noboru *et al.* (1965) and Chan and Ng (1987) suggested that Waldeyer's ring lymphomas, other than nasopharynx, are B-cell in origin and share some of the characteristics of mucosa-associated lymphoid tissue, and nasal lymphomas are almost exclusively PTL. Lin *et al.* (1989) suggested PR is a malignant lymphoma of B-cell origin by immunogenetic analysis. In this study almost all examined cases, except two, showed positive reaction to T-cell marker. The cases which occurred in Waldeyer's ring revealed positive reaction to T-cell marker, like those of the nasal cavity and nasopharynx. An immunoblastic type showed negative reactions to all cell markers examined, but those of T-cell origin in this case can not be excluded because poor differentiation and loss of one or more pan T-cell markers of PR may have resulted in a false negative reaction. PSC showed a stronger positive

reaction to the marker staining than PMLC and it may be influenced by the degree of differentiation. Therefore, PR is considered to be one of the PTL. This study was a retrospective one using formaldehyde-fixed paraffin-embedded tissue sections; however, the subclassification of T-cell lymphocytes still needs a fresh forzen section (Norton and Isaacson 1986; Poppema *et al.* 1987). Further study on frozen sections for subclassification of T-cell lymphocytes will be helpful to clarify the pathogenesis of PR.

Death in a patient with PR occurs after a protracted illness lasting 12 to 18 months after the onset of the active phase and the mean survival is 14 months (Katzenstein *et al.* 1979). The 2/3 of the cases that expired within 6 months in this study were high grade and a case presented initially as dysphagia that rapidly progressed systematically was PMLC. The PMLC, high grade seems to show poorer prognosis than the PSC, low grade (Chott *et al.* 1988); however, a long-term follow-up study of a greater number of patients is needed to generalize this fact.

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