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Pathohistological and immunohistochemical studies on Castleman's disease of the lymph node*

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Summary. Histological and immunohistochemical examinations were carried out on lymph nodes in 9 cases with Castleman's disease. In all cases, there were whorled follicle centers and proliferation of blood vessels. These findings were also considered to be important criteria for diagnosis of the plasma cell type of this disease. The whorled follicle centers often consisted of smaller concentrical structures and contained factor VIII-positive cells. In some cases, there were many small whorled structures surrounding postcapillary venules within the interfollicular areas of lymph nodes. These structures had factor VIII-positive granules indicating their endothelial origin. In 2 cases of the plasma cell type, monoclonal plasma cell proliferation (IgA, λ and IgG, λ, respectively) and cellular atypia were identified. These findings showed that extramedullary plasmacytoma could occur not only in the multicentric form, but also in the solitary form of Castleman's disease. In the lymph node of a case of the hyaline-vascular type, there were scattered tumour nodules consisting mainly of factor VIII-positive, atypical spindle cells suggesting associated Kaposi's sarcoma. It is conceivable that an abnormal immune state plays a role in pathogenesis of Castleman's disease.

Key words: Lymph nodes – Lymphoproliferative disorders – Immunoenzyme technics – Plasmacytoma – Kaposi's sarcoma

Castleman's disease is generally regarded as a benign and localized lesion, though there are different opinions as to whether it is inflammatory or neoplastic in nature. More recently, however, many cases of the multicentric form of Castleman's disease have been reported (Gaba et al. 1978; Bartoli et al. 1980; Mufarriji et al. 1982; Frizzera et al. 1983; Chen 1984). The

* Dedicated to Professor Karl Lennert, Kiel, on the occasion of his 65th birthday

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lymph node lesions of some of these cases showed the transformation into malignant lymphoma. Furthermore, there are some reports on cases of this disease complicated by true neoplasia, such as extramedullary plasmacytoma or Kaposi's sarcoma (Schlosnagle et al. 1982; Kurihara and Hashimoto 1983; Frizzera et al. 1983; Rywlin et al. 1983; Chen 1984). In recent years, therefore, the nature and pathogenesis of Castleman's disease have attracted renewed interest. In order to obtain more precise information on the vascular changes and plasma cell proliferation in this disease, we examined lymph nodes in 9 cases patho-histologically and immunohistochemically.

Material and methods

Clinical data are shown in Table 1. There was no difference in incidence between sexes. The age of the patients ranged from 5 to 84 years and most patients were younger than 60 years of age. The ages of almost one-half of the cases including 2 children were less than 30 years. Some clinical symptoms were found in 3 cases (cases 2, 4, and 9); haematuria in case 2, fever, hyperglobulinaemia (IgG, IgM, and IgA), anaemia and liver dysfunction in case 4, and thrombocytopaenic purpura in case 9. The lymph node lesions were located in various sites; posterior mediastinum (2 cases), side of the neck (3 cases), submaxillary (2 cases), inguinal (1 case) and axillary (1 case) lymph nodes. The typical lesions in 5 cases were solitary, though there were sometimes surrounding lymph nodes with slight enlargement. However, 2 or 3 adjacent tumors were seen in 4 cases (cases 4, 5, 6, and 7). The size of lesions varied from 1 to around 10 cm.

The tissues from the lesions were fixed in 10% formalin, embedded in paraffin, cut at 3–5 μ, and stained with haematoxylin and eosin, Giemsa, PAS, and Gomori's reticulin stains.

Immunohistochemical studies of intracytoplasmic IgG, IgM, IgA, k and λ light chains, and of factor VIII were performed using the unlabelled antibody peroxidase (PAP) method as described by Sternberger (1979). Sections incubated with normal swine serum or phosphate-buffered saline were used as controls. In case 9, lysozyme, S100 protein, α-antitrypsin and α-antichymotrypsin were also examined by means of the PAP-method.

Table 1. Clinical and morphological findings

Case No.	Sex	Age	Clinical symptoms	Lymph node lesions		Size
				Location	Number	
1	M	47	–	R. Side neck	1	Pigeon's egg
2	F	10	Haematuria	R. Submaxillar	1	Pigeon's egg
3	M	48	–	R. Inguinal	1	Thumb
4	F	5	Fever, anaemia, hyperglobulinaemia, liver dysfunction	Posterior mediastinum	2	Fist
5	M	54	–	L. Axillar	2	Hen's egg
6	M	84	–	L. Side neck	3	Cherry
7	F	25	–	L. Side neck	3	Hen's egg
8	M	60	–	L. Submaxillar	1	Thumb
9	F	29	Thrombocytopaenia, purpura	Posterior mediastinum	1	Fist

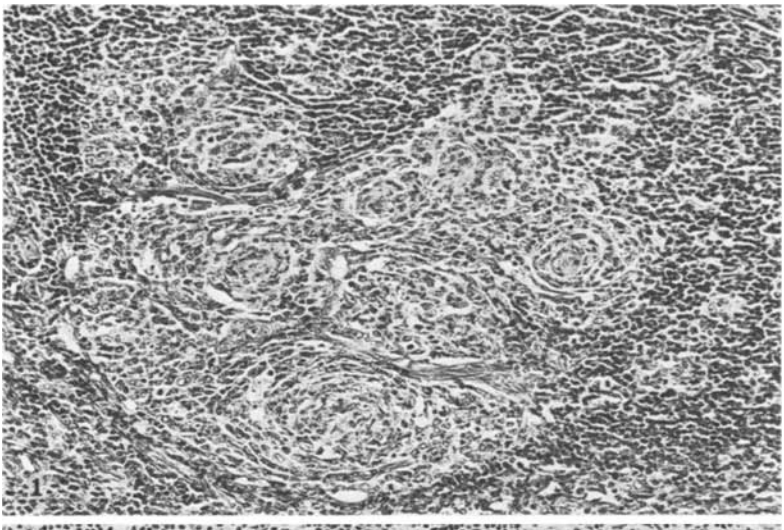
Results

Patho-histological findings

Histlogically, 7 of our 9 cases belonged to the hyaline-vascular type. In the lesions of this type, there were numerous, evenly distributed lymph follicles. In most cases they were large but were relatively small in cases 5 and 9. The boundaries of the follicles were well defined. Whorled centers resembling Hassall's bodies were found in many lymph follicles, consisting of spindle-shaped cells. It was very striking that several centers were often observable within one lymph follicle. Furthermore, there were large, irregularly shaped follicle centers consisting of several small whorled structures (Fig. 1). The centers had some penetrating capillaries with tall endothelial cells and hyalinized wall. In the follicle center, there were no macrophages, while a small number of immunoblasts, centroblasts, and argyrophil fibers were seen.

The interfollicular areas had a large number of postcapillary venules often showing anastomoses. Their endothelial cells showed conspicuous swelling, so that the vascular lumen was almost obliterated. Postcapillary venules, usually located in the interfollicular areas only, were often observed within the lymph follicles (Fig. 2). Furthermore, it is noteworthy that many whorled structures resembling Hassall's bodies were seen also outside the lymph follicles, namely in the interfollicular areas. These structures were formed along the postcapillary venules and surrounded by a narrow rim of concentrically arranged lymphocytes. In PAS-stained sections, many venules with tall endothelial cells were identifiable within these structures (Fig. 3). They often revealed funnel- or fan-shaped openings into the whorled structure. The wall of the postcapillary venules was often thickened and hyalinized. In case 9, several pea-sized, well demarcated, round or irregularly shaped nodules were scattered in the interfollicular areas. They consisted of interlacing spindle-shaped cells (Fig. 4). By means of the Gomori's impregnation method it was established that these nodules contained numerous venules. There were many atypical mono- and multinuclear giant cells with hyperchromatic nuclei and distinct nucleolei within the nodule (Fig. 5).

Two of 9 cases belonged to the plasma cell type. To diagnose this type, our attention has been given to the intensity of plasma cell infiltration, because there were no essential differences in the change of the lymph follicles and other tissue structures between both histological types. In case 1, a marked proliferation of plasma cells was seen in the interfollicular areas of the central part of the lymph node. There were also numerous large lymph follicles with the typical whorled centers in this part. The peripheral part of the lymph node was depressed and contained less plasma cells and lymph follicles than the central part. Although most of the proliferated plasma cells had abundant cytoplasm and small eccentric nucleus, there were some plasma cells with a larger nucleus or 2–3 nuclei. Many lymphocytes were scattered between plasma cells. There were numerous postcapil-



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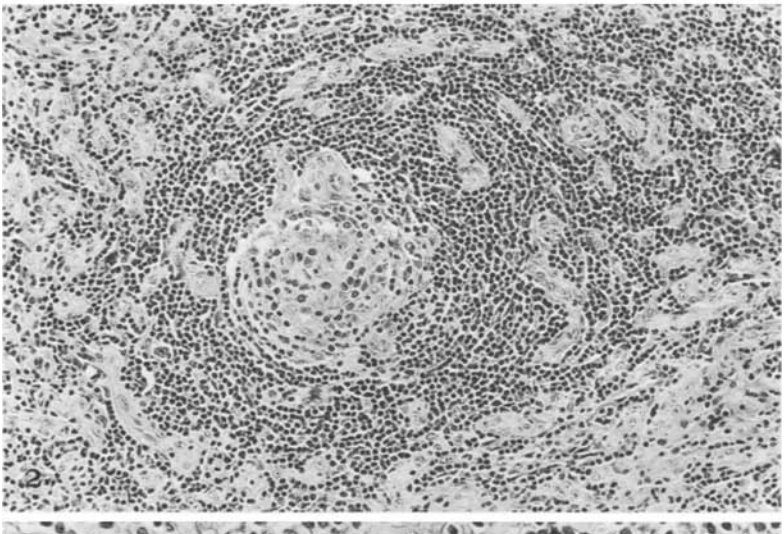

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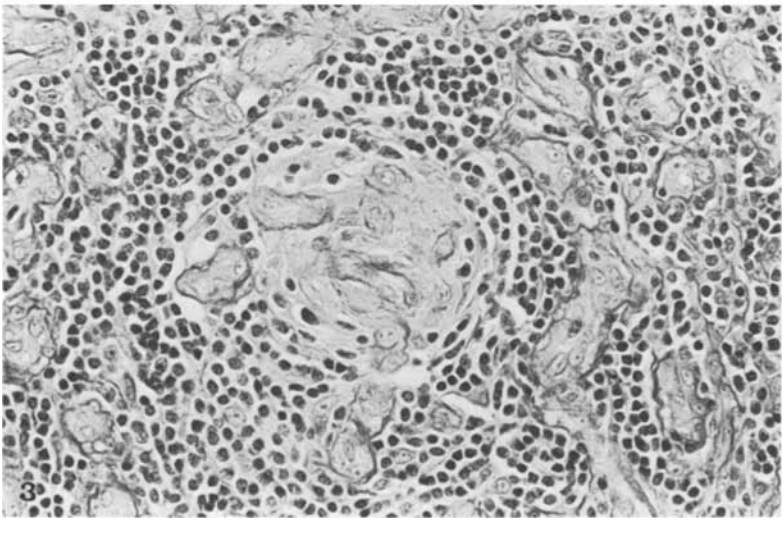

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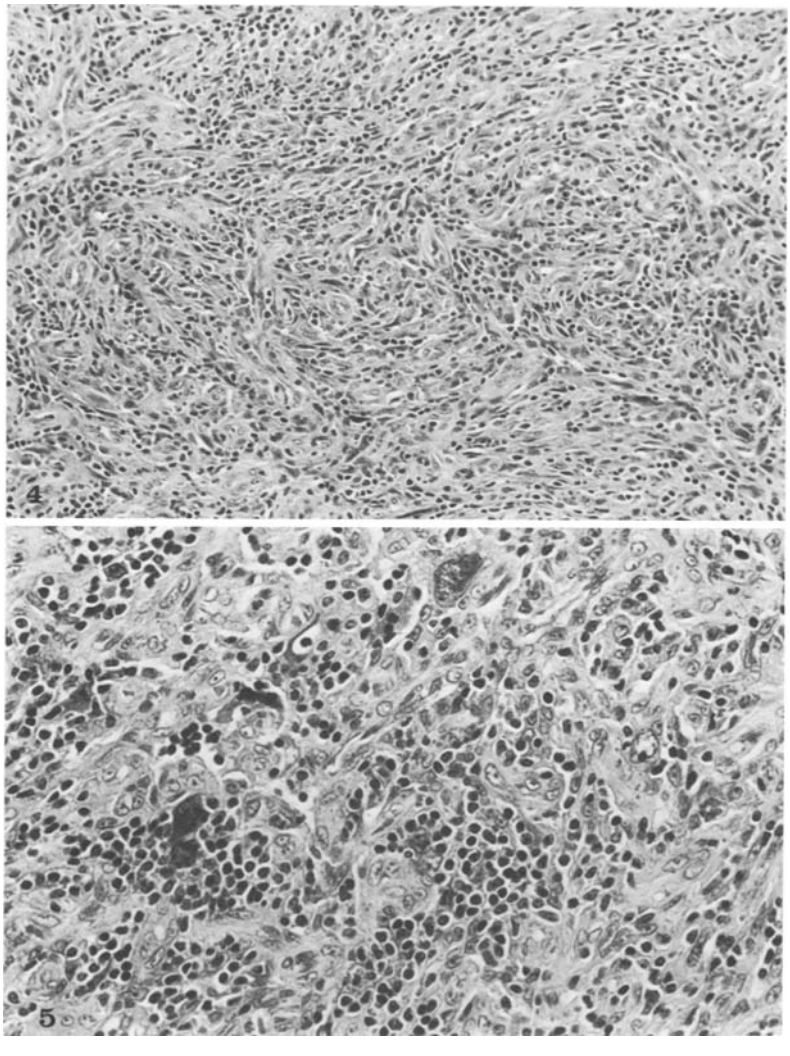

Fig. 4. Tumorous proliferation of spindle-shaped cells in lymph node. H.E., × 50

Fig. 5. Atypical cells in proliferation area of spindle-shaped cells. H.E., × 100

Fig. 1. Large, irregularly shaped follicle centers consisting of many whorled structures. H.E., × 50

Fig. 2. Whorled center and many postcapillary venules in lymph follicle. H.E., × 50

Fig. 3. Postcapillary venules in small whorled structure in the interfollicular area. PAS, × 100

Table 2. Histological and immunohistochemical data

Case No.	Histological type	Intracytoplasmic immunoglobulins									
		Follicle center					Interfollicular area				
		A	M	G	k	λ	A	M	G	k	λ
1	Plasma cell type	±	+	+	+	+	++++	++	++	++	++++
2	Hyaline-vascular type	−	±	±	+	+	±	+	+	+	+
3	Plasma cell type	−	+	+	+	+	+	+	++++	+	++++
4	Hyaline-vascular type	+	+	+	+	+	+	+	++	++	++
6	Hyaline-vascular type	−	+	+	+	+	+	++	++	++	++
7	Hyaline-vascular tpye	−	+	+	+	+	+	+	++	+	+
8	Hyaline-vascular type	−	+	+	+	+	++	+	+	+	+
9	Hyaline-vascular type	+	+	+	+	+	++	++	++	++	++

lary venules, sparse Russell's bodies and hyalinized tissues in the interfollicular areas. In case 3, there was a well-demarcated tumor occupying the central part of the lymph node. This lesion consisted of diffuse and dense proliferation of plasma cells. The plasma cells varied in size and most of them had abundant cytoplasm and relatively large nucleus with a distinct nucleolus, whereas some plasma cells had narrow basophilic cytoplasm and a large hyperchromatic nucleus. Multinuclear plasma cells and mitotic figures were frequently observed. Within the lesion there was a marked increase in argyrophil fibers forming a fairly dense network. Only a few atrophic lymph follicles with small whorled centers were seen in the tumor, while many large follicles with multiple whorled centers presented at the margin and surrounding of this lesion.

Immunohistochemical findings

Using the PAP method we examined intracytoplasmic immunoglobulins and factor VIII in 8 of 9 cases. The results of our examination on intracytoplasmic immunoglobulins are given in Table 2. In 6 cases of the hyaline-vascular type, scattered or grouped plasma cells with positive staining for IgG, IgM, IgA, and k and λ light chains were seen in the interfollicular areas of the lymph nodes. There were no marked differences in the distribution of the positive cells between these stainings, indicating a polyclonal pattern of plasma cell infiltration in these cases. Immunohistochemical findings in the interfollicular areas of 2 cases with the plasma cell type were, however, quite different from those in the hyaline-vascular type. In case 1, most plasma cells which proliferated densely in the interfollicular areas revealed intense positive reaction with IgA and λ light chain stainings, whereas only a small number of positive cells with IgM, IgG, and k light chain stainings was seen. In case 3, most plasma cells showed intense positivity for IgG and λ light chain stainings, while the number of positive cells with IgA, IgM, and k light chain staining was scanty. The plasma cells with

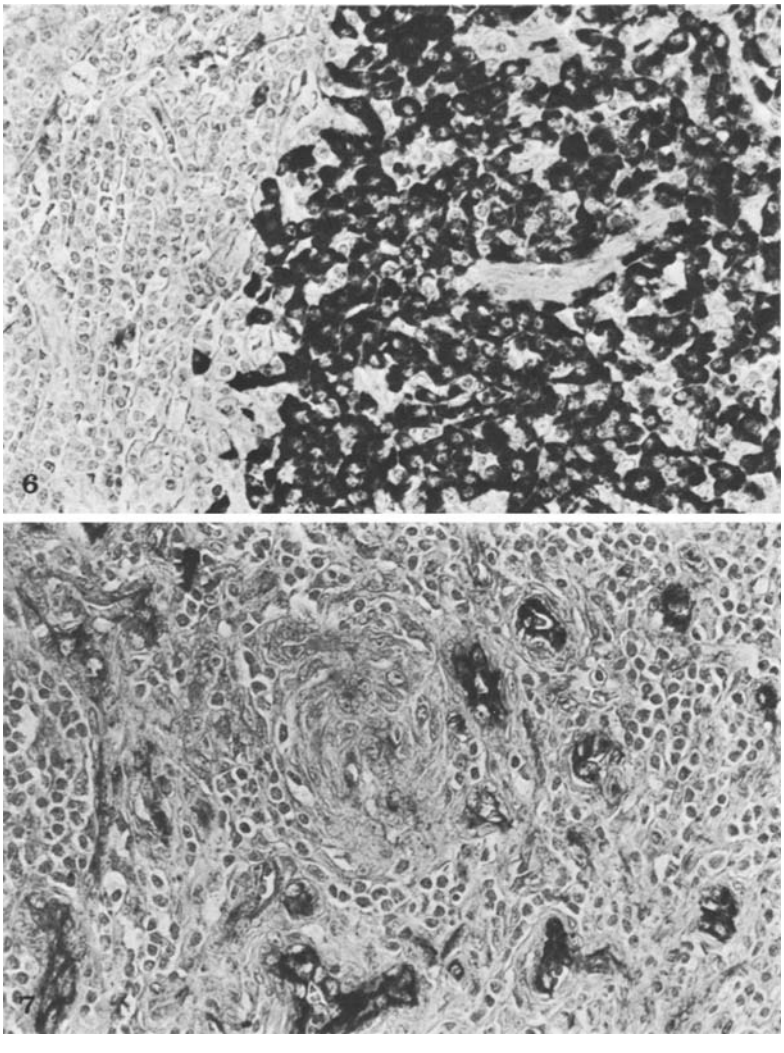

Fig. 6. Lymph node stained for λ light chains. Sharp demarcated tumourous proliferation of positive plasma cells. $\times 100$

Fig. 7. Lymph node stained for factor VIII. Positive granula in endothelial cells of postcapillary venules and in small whorled structure. $\times 100$

positive staining for IgG and λ light chains formed a tumor showing a sharp boundary (Fig. 6). On the basis of the immunohistochemical results we concluded that there was a monoclonal proliferation of plasma cells in these 2 cases. In all 8 cases, there were in general no or only a very few immunoglobulin positive cells in the follicle centers. However, in some follicle centers, such cells were found in considerable numbers. The plasma cells in the follicle centers showed positive reaction with IgG, IgM, k and

λ light chain stainings, whereas they often revealed negativity for IgA staining.

The cytoplasm of endothelial cells of interfollicular postcapillary venules showed a strong positive staining for factor VIII, while endothelial cells of capillaries penetrating into the follicle centers were weakly positive. Some of the large pale cells forming whorled follicle centers contained definitely factor VIII-positive granules. Furthermore, many factor VIII-positive cells were found in the whorled structures around postcapillary venules in the interfollicular areas (Fig. 7). These cells showed no distinct positivity for lysozyme, S100, α_1-antitrypsin and α_1-antichymotrypsin stainings. Excepting atypical bizarre giant cells, spindle-shaped or polygonal cells forming nodules in the lymph node of case 9 often demonstrated positivity with factor VIII staining. The atypical giant cells showed positivity neither with lysozyme, S100, α_1-antitrypsin, and α_1-antichymotrypsin stainings nor IgG, IgM, IgA, k and λ light chain stainings.

Discussion

Keller et al. (1972) stated that there were large follicles with normally appearing or hyperplastic centers without vascularization and hyalinization in the plasma cell type of Castleman's disease. They regarded prominent and dense proliferation of plasma cells in the interfollicular areas as the most important criterion for diagnosis of Castleman's disease, plasma cell type. However, Lennert (1979) and Sakuma and Wakasa (1981) pointed out that prominent plasma cell infiltration in the interfallicular areas and conincident lymph follicle hyperplasia were often observable in various diseases, such as rheumatic lymphadenitis, and therefore could not be regarded as a characteristic finding for the Castleman's disease. In our 2 cases of the plasma cell type, apart from plasma cell infiltrations in the interfollicular areas there were characteristic whorled lymph follicle centers and vascular proliferations inside and outside follicles. In our view, the plasma cell type of Castleman's disease can not be diagnosed without changes other than plasma cell infiltration.

Primary extramedullary plasmacytoma only rarely appear in the lymph node. In the differential diagnosis between neoplastic and non-neoplastic plasma cell proliferation, immunohistochemical findings are most important; monoclonal intracytoplasmic immune antibodies are demonstrable in the neoplastic plasma cells. Ohmori et al. (1983) have pointed out that the general lymph node changes outside the plasmacytoma in their case were very similar to those of the plasma cell type fo Castleman's disease. This observation suggest that primary plasmacytoma can arise in the lymph nodes of Castleman's disease. Actually, 3 cases of Castleman's disease complicated by extramedullary plasmacytoma have been reported recently (Motoori et al. 1981; Schlosnagle et al. 1982; Kurihara and Hashimoto 1983). In all these cases, Castleman's lesions were multicentric and there were tumours consisting of plasma cells in lymph nodes which otherwise showed the typical changes of Castleman's disease. The proliferating plasma cells

revealed variable cellular atypia. No, or only a few lymph follicles were seen within the tumours. Using the PAP-method the monoclonal nature of intracytoplasmic immunoglobulins was established in all cases. A malignant course of the tumours was not seen. In our 2 cases with solitary Castleman's disease, plasma cell type (cases 1 and 3), we demonstrated apparent monoclonal plasma cell proliferation with cellular atypia indicating a neoplastic process. This observation shows that monoclonal neoplastic plasma cell proliferation can occur not only in the multicentric, but also in the solitary form of Castleman's disease.

Harigaya et al. (1975) examined whorled follicle centers electron microscopically and pointed out that they consisted mainly of dendritic reticulum cells. However, our immunohistochemical examination revealed that the whorled centers contained some factor VIII-positive cells. Furthermore, as Lennert (1979) has already described, we also found many postcapillary venules within the lymph follicles which usually presented only in the interfollicular areas. Nevertheless, in some of our cases small whorled structures were found also outside the lymph follicles, that is in the interfollicular areas. These structures showed a close relationship to the postcapillary venules and were surrounded by concentrically arranged lymphocytes. By means of the PAP-method we demonstrated that many cells in these structures had factor VIII-positive granules indicating their endothelial origin. It is considered, therefore, that endothelial cells of small blood vessels play an important role in the formation of the whorled structures in the Castleman's lesion.

Fisher et al. (1970) and Hirasawa et al. (1972) found atypical giant cells in lymph nodes of Castleman's disease and supposed potential malignancy of this disease. Recently, several cases have been reported, in which both changes of Castleman's disease and of Kaposi's sarcoma simultaneously presented in the same lymph node (Frizzera et al. 1983; Rywlin et al. 1983; Chen 1984). Rywlin et al. (1983) have pointed out that the frequency of combination of these diseases was higher than by chance alone. They supposed that both diseases represented different morphological expressions against a common aetiological factor, whereas Chen (1984) considered that the abnormal immune state in Castleman's disease was related to the development of Kaposi's sarcoma. In one of our 9 cases with Castleman's disease, there were several, bean-sized, well demarcated tumor consisting of spindle-shaped cells. These cells were arranged in an interlacing pattern and formed many narrow vascular channels. There were often atypical polygonal or spindle-shaped cells with large hyperchromatic nuclei and conspicuous nucleolei. Atypical multinuclear giant cells were seen in these lesions. As to the histogenesis of Kaposi's sarcoma Nadji et al. (1981) have established immunohistochemically and electron microscopically that this sarcoma largely consisted of tumour cells of endothelial origin. In our case, spindle-shaped or polygonal cells in the tumour lesion revealed apparent positivity with factor VIII staining, though no positive granules could be found in the atypical bizarre giant cells. Histological pictures of the remaining part of the lymph node were in accord with the findings of Castleman's disease.

On the basis of our observation, it is suspected that this case represents the early stage of Kaposi's sarcoma arising in the Castleman's lesion. Fayemi and Toker (1975) and Lott and Davies (1983) have called attention to the occurrence of lymph nodal angiomatosis or haemangiomatoid lesions and stressed that they must be carefully distinguished from Kaposi's sarcoma in lymph nodes. According to these authors, cellular atypism, mitotic figures and haemosiderin deposition are not observable in angiomatosis and haemangiomatoid lesions. In our case, lymph nodal angiomatosis and haemangiomtoid lesions were excluded, because the above mentioned findings were recognizable.

It is generally known that Castleman's disease, especially the multicentric form, very often accompanies various symptoms related to abnormal immunological states, such as hyperglobulinaemia, thrombotic thrombocytopaenic purpura, amyloidosis, or the nephrotic syndrome (Keller et al. 1972; Bartoli et al. 1980; Frizzera et al. 1983; Chen 1984). Two of our cases with solitary Castleman's disease showed such clinical symptoms. Furthermore, prominent proliferation of plasma cells in the plasma cell type suggest the presence of immunological abnormality in this disease. Therefore, it is conceivable that immunological disturbances may play an important role in pathogenesis of Castleman's disease. The frequent association with Kaposi's sarcoma also provide support for this view, because this tumour, often develops in abnormal immune states (Ulbright and Santa Cruz 1981; Chen 1984; Gurda et al. 1984; Hocking et al. 1984).

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