Virchows Arch [Pathol Anat] (1985) 405:473–481

Virchows Archiv A

Follicular malignant non-Hodgkin's lymphoma with pronounced plasmacytic differentiation: A plasmacytoma-like lymphoma *

U. Schmid[1], **J. Karow**[2], **and K. Lennert**[3]

[1] Institut für Pathologie, Kantonsspital, CH-9007 St. Gallen, Switzerland
[2] Abteilung für Hämatologie und Onkologie, Universitätsklinikum Steglitz, Hindenburgdamm 30, D-1000 Berlin 45
[3] Institut für Pathologie, Klinikum der Christian-Albrechts-Universität, Hospitalstrasse 42, D-2300 Kiel, Federal Republic of Germany

Summary. A case of follicular centroblastic-centrocytic lymphoma with an unusually pronounced plasmacytic component occurring in the gingiva and cervical lymph nodes of a 74-year-old male patient is described. Immunohistological analysis revealed a monotypic intracytoplasmic immunoglobulin pattern (IgM/λ). The relation between follicular malignant non-Hodgkin's lymphomas and extramedullary plasmacytome is discussed. In the present case the tumour may represent the development of an autonomous plasma cell clone within a follicular centroblastic-centrocytic lymphoma.

Key words: Follicular non-Hodgkin's lymphoma – Centroblastic-centrocytic lymphoma – Non-Hodgkin's lymphoma with plasmacytic component – Plasma cell differentiation – Extramedullary plasmacytoma

Introduction

Non-Hodgkin's lymphomas and typical plasmacytomas are known to occur primarily in lymph nodes (Lennert et al. 1978). Lymph node plasmacytoma is also a non-Hodgkin's lymphoma in the narrow sense and belongs to the group of extramedullary plasmacytomas. These tumours most frequently occur in the head and neck region and are seldom localized in lymph nodes primarily. In the files of the Lymph Node Registry in Kiel, primary plasmacytomas of lymph nodes represent only 0.5% of all malignant lymphomas and 0.8% of non-Hodgkin's lymphomas (Lennert et al. 1978). Among the non-Hodgkin's lymphomas several entities, especially immunocytoma and B-immunoblastic lymphoma, show a relationship to the plasma cell reaction.

* Dedicated to Professor Dr. F. Gloor, St. Gallen, on the occasion of his 60th birthday

Offprint requests to: U. Schmid at the above address

In these tumours persistent plasma cell maturation can be observed. Typical follicular centre-derived non-Hodgkin's lymphomas, such as centroblastic-centrocytic lymphoma, may also show plasmacytic differentiation. In this report a follicular non-Hodgkin's lymphoma with an unusually marked plasmacytic component will be described.

Material and methods

The lymph node biopsy was fixed in formalin and embedded in paraffin. Sections of 3–4 μm were cut and stained with haematoxylin and eosin (H&E), Giemsa, periodic acid Schiff (PAS), silver impregnation (Gomori) and Congo red. The diagnosis on the lymph node biopsy was substantiated by immunoperoxidase staining for cytoplasmic immunoglobulin (CIg) using the modification of Mepham et al. (1979). Antisera against IgA, IgG, IgM and κ and λ chains were used. Imprints were stained with Pappenheim (May-Grünwald-Giemsa) and several cytochemical methods (acid esterase, acid phosphatase, PAS and diaminopeptidase IV [DAP IV]).

Results

Clinical findings. A 74-year-old male patient presented with an indolent mass in the right mandibular region that had been growing continuously for 6 months. The anterior vestibule of the mouth was elevated by the tumour without radiological evidence of bone destruction. The submandibular lymph nodes were bilaterally enlarged. No other lymphadenopathy was noted. Radiological examination did not reveal osteopathic lesions. Bone marrow smears were normal. With the exception of slight leucocytosis (10000/μl) no abnormalities in the peripheral blood picture were noted. The ESR was elevated (18/36 mm/h). Immunoelectrophoresis showed a polyclonal increase in IgM. Hepatomegaly, splenomegaly, or lymphadenopathy was not observed in an abdominal computer tomograph. Needle biopsies of both right and left hepatic lobes did not reveal tumour infiltration. When the histological diagnosis was established, the patient received local radiotherapy of the mandibular lesion and submandibular lymph nodes.

Six months later the patient was treated for an inflammatory pseudotumour in the left lower abdominal region, most probably caused by a perforated large bowel diverticulum. At this time he was clinically free of tumour in the mandibular region. No monoclonal immunoglobulin could be found.

The patient died two years later. A palpable mass was found in the large bowel near the hepatic flexure. The liver was enlarged and of nodular appearance. Lymphocytosis was noted in the peripheral blood. No autopsy was performed.

Morphological findings. The architecture of the investigated supraclavicular lymph node was completely effaced by a tumour that consisted predominantly of medium-sized lymphoid follicles and infiltrated the lymph node capsule and the surrounding soft tissue (Fig. 1). The neoplastic follicles were mostly arranged in layers and consisted of both follicular centre cells and atypical plasma cells (Fig. 2) with enlarged nuclei containing prominent nucleoli. In the centre of these follicles foci of centroblasts, centrocytes

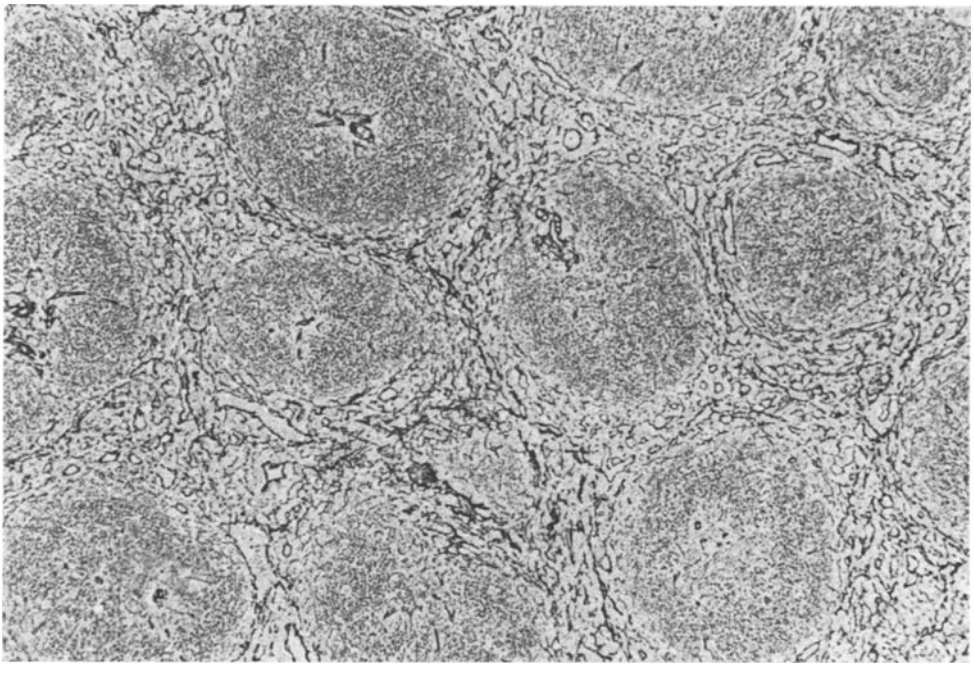

Fig. 1. Follicular pattern of the tumour. Reticulin staining, ×56

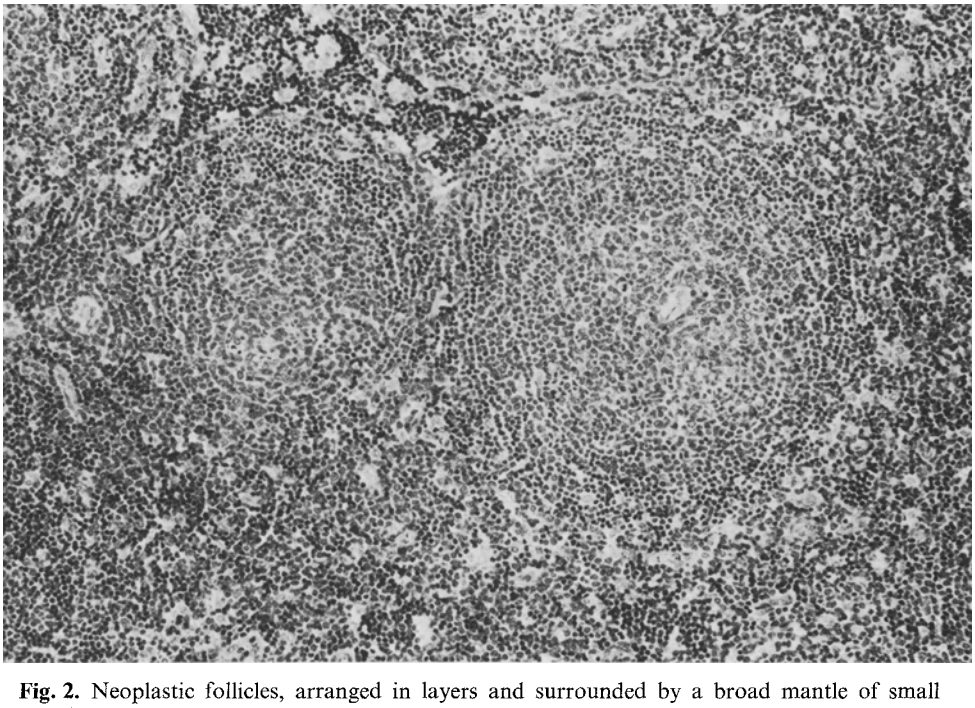

Fig. 2. Neoplastic follicles, arranged in layers and surrounded by a broad mantle of small lymphocytes. Giemsa, ×140

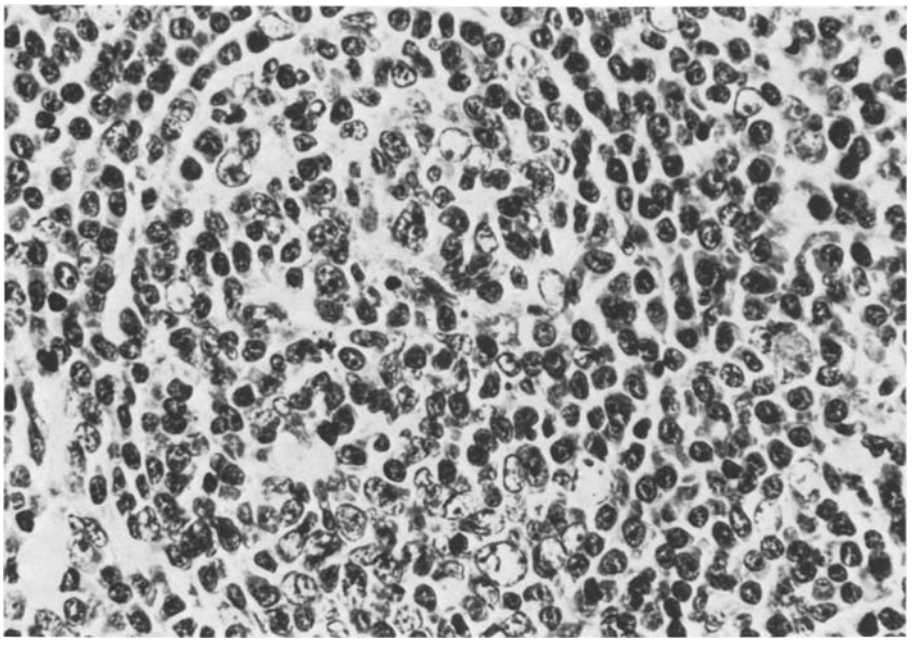

Fig. 3. Germinal centre containing centroblasts and centrocytes, surrounded by atypical plasma cells. Giemsa, × 560

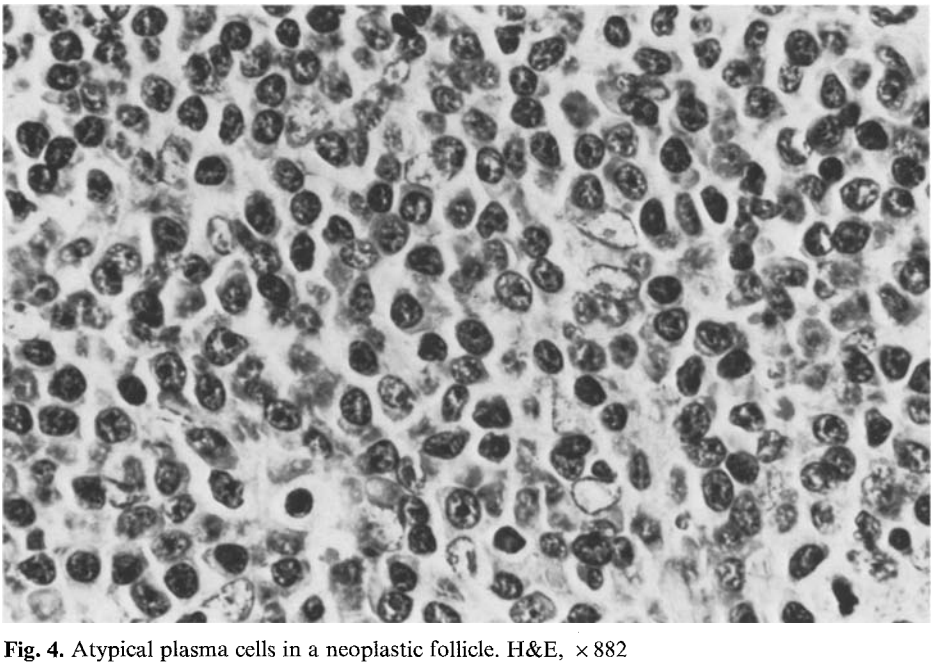

Fig. 4. Atypical plasma cells in a neoplastic follicle. H&E, × 882

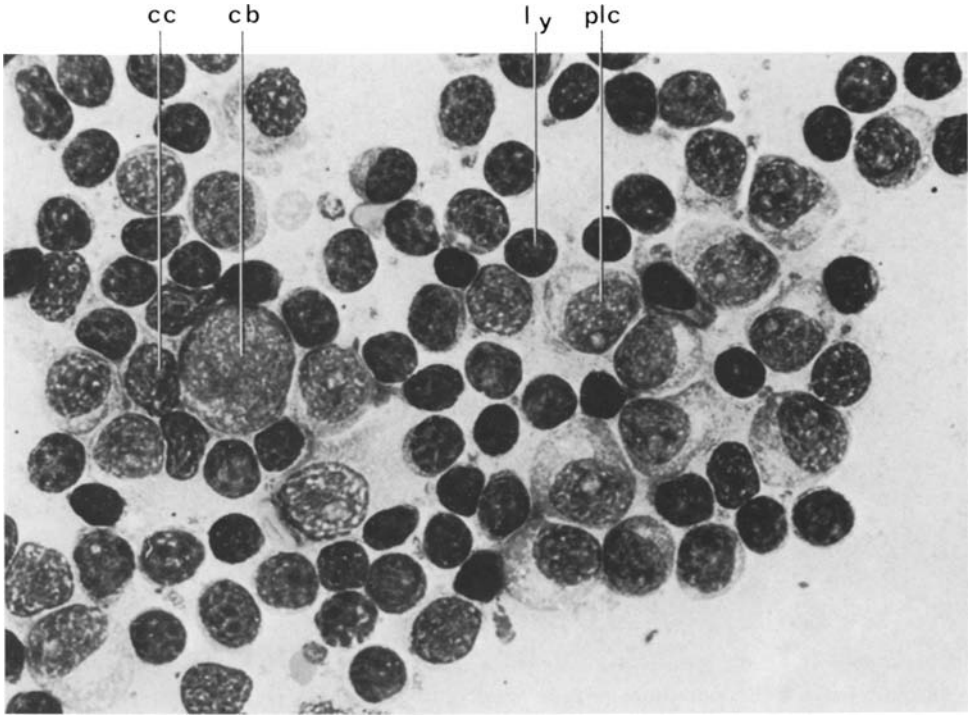

Fig. 5. Lymph node imprint showing many atypical plasma cells (*plc*), some small lymphocytes (*ly*) and a centroblast (*cb*) surrounded by a few centrocytes (*cc*). Pappenheim, × 882

and some macrophages could be observed (Fig. 3). Immunoblasts were only occasionally seen. This area was surrounded by a concentrically arranged layer of atypical plasma cells (Fig. 4). The cytoplasm of these medium-sized plasma cells showed diffuse PAS activity and revealed a perinuclear halo in some instances. The round nuclei were larger than those of typical plasma cells. Chromatin was moderately coarse and sometimes condensed near the nuclear membrane. Most cells showed a solitary nucleolus but a few cells had several medium-sized nucleoli. In addition to these plasma cells, several atypical cells with cytoplasmic features of plasma cells and nuclear characteristics of lymphoid cells were observed. The nuclear configuration resembled that of centrocytes. There was moderate mitotic activity. The atypical plasma cells contained a few intracytoplasmic and intranuclear PAS-positive globules. Some typical centroblasts and centrocytes were found interspersed throughout the area. The external layer of these follicles consisted of concentrically arranged small lymphocytes comparable to the mantle zone of reactive lymphoid follicles. The interfollicular areas showed a dense reticulum framework and were highly vascularized. They contained a moderate number of atypical plasma cells, many small lymphocytes, a few immunoblasts, typical plasma cells and several mast cells. There were some deposits of hemosiderin pigment. Congo red staining was negative. A biopsy taken

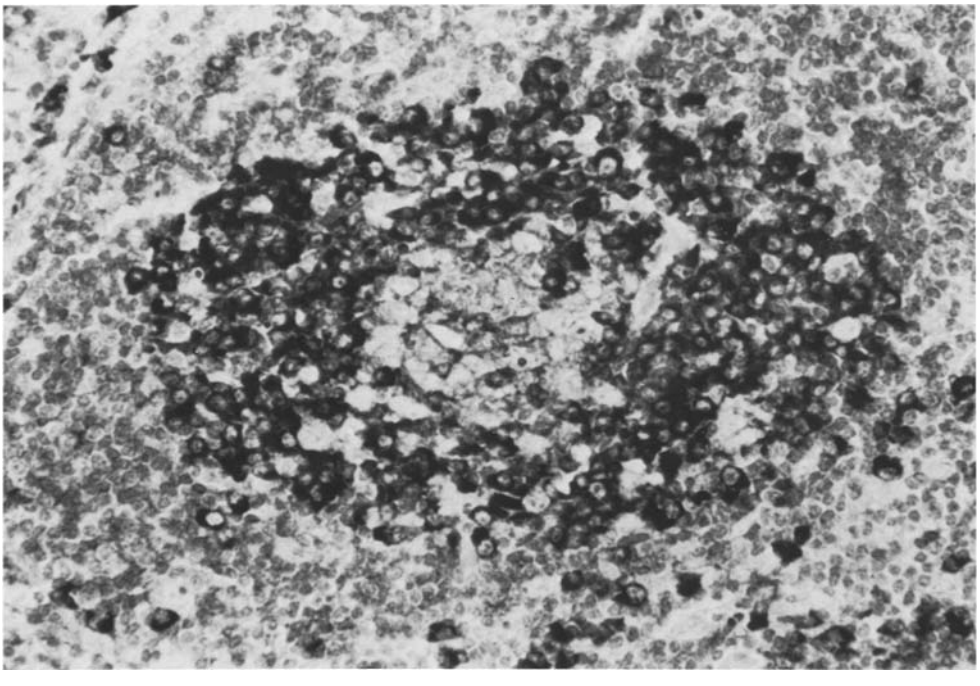

Fig. 6. Follicle immunostained for IgM. Ig-negative germinal centre is surrounded by strongly positive plasma cells (monotypic for IgM/λ). Immunoperoxidase, $\times 350$

from the gingival mass and investigated elsewhere was reported to show the same tumour.

The lymph node imprints revealed a predominance of atypical plasma cells with finely vacuolized cytoplasm and a perinuclear halo (Fig. 5). The PAS reaction was negative. With acid phosphatase staining the cytoplasm showed a moderately positive crescent-shaped reaction product corresponding to the Golgi area. The hyperchromatic nuclei had dense reticular chromatin and solitary medium-sized nucleoli. Centroblasts and centrocytes were occasionally seen among these atypical plasma cells. In addition, a large number of small lymphocytes showing focal acid esterase and acid phosphatase reactions and DAP IV activity was present. These findings correspond to those obtained in a cytological analysis done in the Department of Haematology at the hospital in Berlin where the patient had been treated.

The immunohistological investigations of the lymph node tissue revealed a monotypic CIg pattern (IgM/λ) in the great majority of the atypical plasma cells within the follicular structures as well as between these follicles. CIg was not detected in the centroblasts and centrocytes located in the centre of these follicles (Fig. 6). Some of the centrocytes, centroblasts and immunoblasts interspersed in the plasma cell component did, however, show monotypic Ig. Consequently, immunoperoxidase staining resulted in a very clear demarcation of the CIg-positive plasma cell layer of the follicles (Fig. 6). Some typical mature plasma cells in the interfollicular areas revealed a polytypic Ig pattern.

Discussion

Plasmacytic differentiation in malignant non-Hodgkin's lymphoma with or without monoclonal gammopathy is well known, especially in tumours with a close relationship to the plasma cell reaction such as immunocytoma, immunoblastic lymphoma of B type and plasmacytoma (Stein et al. 1980). Typical germinal centre-derived lymphomas may also exhibit plasmacytic differentiation. This is true for diffuse types more often than for follicular types (Lennert et al. 1978; Bain and Belch 1981). These tumours have been interpreted as borderline lesions between follicular centre cell lymphomas and lymphoplasmacytoid immunocytoma (Stein et al. 1978; Pileri et al. 1983). Recently, Pileri et al. (1983) reviewed 30 cases recorded as borderline lesions between centroblastic-centrolytic lymphoma and immunocytoma. They were able to divide the cases into two groups. The first group consisted of typical centroblastic-centrocytic lymphomas with marked plasmacytic differentiation. The second group of cases in which the tumour grew in a mantle-like fashion around reactive follicles, was quite heterogeneous and contained both immunocytomas and centrocytic lymphomas.

We do not know of any observations of a follicular non-Hodgkin's lymphoma with such a marked degree of plasmacytic differentiation, in combination with a monotypic CIg pattern, as described here. Since the plasma cell component is the predominating feature of this tumour, the question arises whether it represents a typical germinal centre cell lymphoma or a follicular type of extramedullary plasmacytoma. The great majority of extramedullary plasmacytomas have been found to arise in the upper respiratory tract and oral cavity (Poole and Marchetta 1968; Medini et al. 1980; Batsakis 1983). Lymph nodes are also occasionally reported to be the site of origin of such tumours (Jequier-Doge et al. 1947; Hirscher 1953/54; Nelson and Lyons 1957; Wiltshaw 1976; Bruce et al. 1980). In all the cases of plasmacytoma we have seen and in similar cases mentioned in the literature, the tumour showed a diffuse growth pattern and was composed of a pure monotypic plasma cell population (Jequier-Doge et al. 1947; Rowlands and Shaw 1954; Poole and Marchetta 1968; Gaston et al. 1969; Wiltshaw 1976; Lennert et al. 1978; Bruce et al. 1980).

In the present case several findings indicate that the tumour was of germinal centre origin. The most important indications were the follicular pattern and the presence of centrocytes and centroblasts not only in the centre of the neoplastic follicles but also among the plasma cells. The interfollicular areas that were rich in reticulin fibres and capillaries corresponded to the T areas seen in typical follicular non-Hodgkin's lymphomas (Kaiserling 1976). The large number of small lymphocytes with DAP IV activity and focal acid phosphatase and acid esterase reactions (interpreted as T cells [Feller and Parwaresch 1980]) may have a relationship to these interfollicular areas. Similar findings have been reported in studies of cell suspensions and imprints of follicular non-Hodgkin's lymphomas of centroblastic-centrocytic type (Jaffe et al. 1974; Leech et al. 1975; Lennert et al. 1978; Stein et al. 1978). Although recent immunohistological studies of ophthalmic immunocytoma (Molenaar et al. 1983) and immunocytoma developing in

myoepithelial sialadenitis (Schmid et al. 1982) suggest a close relationship between germinal centres and lymphoplasmacytoid immunocytoma, the tumour described here represents a different entity. In all cases of immunocytoma immunoblasts are an essential component; this is in accord with the transformation of lymphocytes into plasma cells. Since only a few immunoblasts were present in our case, marked plasma cell differentiation via immunoblasts appears to be unlikely. Hence we may speculate on the possibility of plasmacytic transformation of germinal centre cells. This hypothesis is supported by an electron microscopic finding reported by Kaiserling (1976), viz.: the presence of ergastoplasm in centrocytes. Centroblastic-centrocytic lymphoma may show plasmacytoid differentiation (Stein 1975), and CIg has been demonstrated in such cases (Taylor 1976; Pascali et al. 1980; Stein et al. 1980; Tolksdorf et al. 1980; Vernon and Lewin 1980). The presence of intranuclear PAS-positive globules has also been reported (Lennert et al. 1978). The so-called signet ring cell lymphomas represent more proof of the ability of germinal centre cell lymphoma cells to synthesize and secrete Ig (Kim et al. 1978). Ig production in such tumours takes place in typical follicular centre cells, however, and not in plasma cells, whereas in our case CIg was demonstrated in plasma cells and no signet ring cells were found.

In our opinion, this tumour indicates that plasmacytic transformation may take place in follicular centroblastic-centrocytic lymphoma. This would correspond to what happens in reactive germinal centres after antigen stimulation. Recent immunohistological studies (Lennert and Stein 1982) have shown the presence of Ig-containing centrocytes in reactive germinal centres, suggesting that germinal centres are capable of producing plasma cell precursors. This also applies to the present case of follicular lymphoma. Plasmacytic differentiation, which usually occurs in the interfollicular area, appeared to have advanced into the germinal centres. Because of the predominance of atypical plasma cells and the presence of relatively few typical germinal centre cells in the neoplastic follicles, a continuous supply of plasma cells originating from germinal centre cells seems unlikely. We think it is more likely that the malignant tumour represented the development of an autonomous plasma cell clone within a follicular centroblastic-centrocytic lymphoma.

Acknowledgements. We are indebted to Mrs. Martha Soehring and Mr. James Heywood for preparation of the manuscript.

References

Bain GO, Belch A (1981) Nodular mixed cell lymphoma with monoclonal gammopathy. Am J Clin Pathol 76:832–837

Batsakis JG (1983) Plasma cell tumours of the head and neck. Ann Otol Rhinol Laryngol 92:311–313

Bruce IA, Isaacson P, Billings JA (1980) Plasmacytoma of lymph nodes. Cancer 46:340–346

Feller AC, Parwaresch MR (1980) Zytochemische Darstellung der Blasten bei akuter T-lymphoblastischer Leukämie mit Hilfe der Glycyl-prolyl-4-methoxy-beta-naphthylamid-Peptidase (DAP IV). Klin Paediatr 192:150–153

Gaston EA, Dollinger MR, Strong EW, Hajdu SI (1969) Primary plasmacytoma of lymph nodes. Lymphology 2:7–15

Hirscher H (1953/54) Über extramedulläres lympho-reticuläres diffuses Plasmozytom. Folia Haematol (Leipz) 72:74–86

Jaffe ES, Shevach EM, Frank MM, Berard CW, Green I (1974) Nodular lymphoma. Evidence for origin from follicular B-lymphocytes. N Engl J Med 290:813–819

Jequier-Doge E, Nicod JL, Chapuis JP (1947) Un cas de plasmocytome a localisation ganglionnaire observé cliniquement pendant plus de 6 ans et controlé anatomiquement. Schweiz Med Wochenschr 77:186–190

Kaiserling E (1976) Electronenmikroskopische Befunde bei Non-Hodgkin-Lymphomen. In: Löffler H (ed) Maligne Lymphome und monoklonale Gammopathien. Hämatologie und Bluttransfusion, vol 18. Lehmanns, München, pp 185–198

Kim H, Dorfman RF, Rappaport H (1978) Signet ring cell lymphoma. A rare morphologic and functional expression of nodular (follicular) lymphoma. Am J Surg Pathol 2:119–132

Leech JH, Glick AD, Waldron JA, Flexner JM, Horn RG, Collins RD (1975) Malignant lymphomas of follicular center cell origin in man. I. Immunologic studies. J Natl Cancer Inst 54:11–21

Lennert K, Stein H (1982) The germinal centre: morphology, histochemistry, and immunohistology. In: Goos M, Christophers E (eds) Lymphoproliferative Diseases of the Skin, Springer, Berlin Heidelberg, pp 3–15

Lennert K, in collaboration with Mohri N, Stein H, Kaiserling E, Müller-Hermelink HK (1978) Malignant lymphomas other than Hodkin's disease. (Handbuch der speziellen pathologischen Anatomie und Histologie, vol 1, Part 3B) Springer, Berlin Heidelberg New York

Medini E, Rao Y, Levitt SH (1980) Solitary extramedullary plasmacytoma of the upper respiratory and digestive tracts. Cancer 45:2893–2896

Mepham BL, Frater W, Mitchell BS (1979) The use of proteolytic enzymes to improve immunoglobulin staining by the PAP technique. Histochem J 11:345–357

Molenaar WM, Schwarze EW, Lennert K (1983) An immunological study of germinal centres in four ophthalmic immunocytomas. Virchows Arch [Pathol Anat] 399:141–148

Nelson MG, Lyons AR (1957) Plasmacytoma of lymph glands. Cancer 10:1275–1280

Pascali E, Pezzoli A, Falconieri G (1980) Nodular lymphoma eventuating into lymphoplasmacytic lymphoma with monoclonal IgM/λ, cold agglutinin and Bence-Jones proteinuria. Acta Haematol (Basil) 64:94–102

Pileri S, Rivano MT, Piccaluga A, Lennert K (1983) Borderline lesions between centroblastic-centrocytic lymphomas and immunocytomas of the Kiel classification. Morphofunctional study of 30 cases. Congress on current topics in lymphopathology, Bologna, Oct 1983

Poole AG, Marchetta FL (1968) Extramedullary plasmacytoma of the head and neck. Cancer 22:14–21

Rowlands B, Shaw N (1954) Extramedullary plasmacytoma. Br Med J I:1302–1303

Schmid U, Helbron D, Lennert K (1982) Development of malignant lymphoma in myoepithelial sialadenitis (Sjögren's syndrome). Virchows Arch [Pathol Anat] 395:11–43

Stein H (1975) Zur Characterisierung maligner Lymphome. Morphologie und immunologische Untersuchungen. Habilitation thesis, Kiel 1975

Stein H, Papadimitriou CS, Bouman H, Lennert K, Fuchs J (1978) Demonstration of immunoglobulin production by tumour cells in non-Hodgkin's lymphomas and its significance for their classification. Recent Results Cancer Res 64:158–175

Stein H, Siemssen U, Lennert K (1978) Complement receptor subtypes (C3b and C3d) in lymphatic tissue and follicular lymphoma. Br J Cancer 42:168–182

Stein H, Bonk A, Tolksdorf G, Lennert K, Rodt A, Gerdes J (1980) Immunohistologic analysis of the organization of normal lymphoid tissue and non-Hodgkin's lymphomas. J Histochem Cytochem 28:746–760

Taylor CR (1976) An immunohistological study of follicular lymphoma, reticulum cell sarcoma and Hodgkin's disease. Eur J Cancer 12:61–75

Tolksdorf G, Stein H, Lennert K (1980) Morphological and immunological definition of a malignant lymphoma derived from germinal-centre cells with cleaved nuclei (centrocytes). Br J Cancer 41:168–182

Vernon SE, Lewin KJ (1980) Immunoperoxidase and immunofluorescence in lymph node biopsies. A comparative study. Am J Surg Pathol 4:357–363

Wiltshaw E (1976) The natural history of extramedullary plasmacytoma and its relation to solitary myeloma of bone and myelomatosis. Medicine (Baltimore) 55:217–238

Accepted November 26, 1984