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Neoplastic plasma cells in follicular lymphomas

Clinical and pathologic findings in six cases*

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Summary. Six cases of follicular lymphoma contained an abundant plasma cell component. With immunoperoxidase techniques, this was found to demonstrate monotypic cytoplasmic marking for either K or L Ig light chain in five cases, and for IgA heavy chain only in one case. A histogenetic relationship between follicular center cells and plasma cells was suggested by cell forms morphologically intermediate between these two types and by monotypic plasma cells in the neoplastic follicles. The progressive differentiation of follicular center cells into Ig-secreting cells in these cases is likely to be the result of an alteration of the immunoregulatory mechanisms that usually block the differentiation of follicular lymphomas.

Four of our patients presented with disseminated disease, three had extranodal presentation and four manifested serum paraproteins. Their median survival was 40 months; two of them died of disease. The published data and our own suggest that follicular lymphoma with plasmacytic differentiation is a malignancy of intermediate grade, with survival and clinical features closer to lymphoplasmacytic/lymphoplasmacytoid lymphoma (LP immunocytoma) than to follicular lymphoma.

Key words: Follicular lymphoma – Centroblastic/centrocytic lymphoma – Non-Hodgkin's lymphoma with plasmacytic differentiation

Introduction

The presence of abundant plasma cells is not typical of follicular (nodular) lymphomas. In the differential diagnosis of follicular lymphoid lesions, this feature has been regarded as one piece of evidence in favor of reactive

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

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follicular hyperplasia (Rappaport et al. 1956). Recently, however, Keith et al. (1985) have reported large numbers of reactive (polyclonal) plasma cells in a small proportion (5%) of follicular lymphomas.

More interestingly, the same authors and others (Nemes et al. 1981; Schmid et al. 1984; Vago et al. 1985) have documented rare instances of follicular lymphoma containing a monoclonal plasma cell population. We report here the clinical, histological and immunohistochemical findings in six additional cases of this composite tumour and discuss its histogenesis and biological behavior.

Material and methods

These six cases were culled from the Surgical Pathology and consultation files at the University of Minnesota (four) and at the Mayo Clinic (two). The clinical charts from the four patients diagnosed and treated at these institutions were reviewed. Clinical and follow-up information on the two patients in whom material was seen in consultation (#2 and 3) were obtained through the courtesy of the contributing pathologists. All available histological material on these patients was also reviewed. This included multiple specimens from the original tumour in each case, and additional subsequent lymph nodes biopsies in two (#1 and 4).

In all cases the material had been fixed in formalin and embedded in paraffin. From each block three microns sections were obtained and the following staining procedures were performed: haematoxylin-eosin, periodic acid Schiff (PAS), with and without digestion, and silver impregnation for reticulin. Serial sections were tested for the presence of cytoplasmic immunoglobulin (cIg) (G, A, M, D heavy chains and K and L light chains) according to the avidin-biotin-immunoperoxidase technique (Hsu et al. 1981). All primary antisera were obtained commercially (anti-IgA: Calbiochem-Behring; all others: DakoPatts Co.). They were diluted in 0.05 M phosphate-buffered saline, pH 7.5; optimal dilutions were determined by prior studies on formaldehyde-fixed lymphoid tissue. Biotinylated goat anti-rabbit antiserum (Vectastain Kit) and avidin-biotin-peroxidase complex (Vectastain Kit) were then applied. Sections incubated with normal rabbit serum (in place of the primary antibody) were used as negative controls. Formaldehyde-fixed paraffin-embedded tonsils were used as positive controls.

Results

Clinical findings

The pertinent clinical information on our patients is summarized on Table 1. Three were females and three males. Their age ranged from 47 to 84 years (median 60). Two patients, both with extranodal presentation, had localized disease, four had disseminated disease. Two patients had constitutional symptoms. Laboratory findings were unremarkable in all. Among the four patients in whom serum protein electrophoresis was performed, two manifested a gammopathy. In patient #5 a prominent monoclonal spike was observed and quantitative evaluation of Ig showed serum IgM values of 9270 mg/dl (normal range: 53–375 mg/dl), and IgG and IgA values within the normal range. In patient #6 serum immunoelectrophoresis showed two monoclonal bands, IgMK and IgGK; no monoclonal proteins were found on urine immunoelectrophoresis. Interestingly, this latter patient had clinically and serologically documented systemic lupus erythematosus for 5 years before the diagnosis of lymphoma was made.

Table 1. Clinical findings

Pt. No.	Age/Sex	Organ Involvement	Stage	SEP	Therapy	Response	Further Course	Follow-up	
								Status	Period (months)
1	64/F	4.79: mesent. & retro-peritoneal LNs	IIIA	Nl	CHOP-B	PR	Additional CT: CR in 6.80		
		12.83: abdominal LNs – b.m. suspicious for ML		Nl	COPP	PR	4.84: liver & renal failure	DOD	61
2	47/M	Thyroid mass; paratracheal LN	II_EB	ND	CVPP; RT	CR		A & W	48
3	64/F	Diffuse enlargement of thyroid; paratracheal LNs	II_EA	ND	Subtotal thyroidec-tomy; RT	CR		A & W	31
4	54/M	6.80: abdom. & periph. LNs, bone marrow	IVB	Nl	CVPP	CR	3.82 recurrence; additional CT		
		7.83: abdom. & periph. LNs, liver		ND	M-BACOP	PR			
		2.84: peripheral LNs		Nl	Ara-C; cDDP	PR	3.85 recurrence	A with D	60
5	84/M	Bilateral eyelid masses	IVA	IgM monoclonal	None		14 months later, positive b.m. Subsequent rapid deterioration	DOD	19
6	56/F	Abdom. & periph. LNs; bone marrow	IVA	IgGK IgMK	Chl, P	CR		A & W	19

LN = lymph node; ML = malignant lymphoma; SEP = serum electrophoresis; Nl = normal; ND = not done; C = cyclophosphamide; H or A = doxorubicin; O = vincristine; P = prednisone; B = bleomycin; V = vinblastine; PP = procarbazine, prednisone; RT = local radiation therapy; M = methotrexate; Ara-C = cytosine arabinoside; cDDP = cis-platinum; Chl = chlorambucil; PR = partial response; CR = complete response; CT = chemotherapy; b.m. = bone marrow; DOD = dead of disease; A&W = alive and well; A with D = alive with disease

Table 2. Pathologic findings

Pt. No.	Site of biopsy	Classification of F, ML	Follicles			Interfollicular areas				Immuno-peroxidase	Inclusions		Comments
			PC	IB	Other cells	FCC	PC	IB	Other cells		Number	PAS	
1	LN – 5.79	F, SC	±	++		+	±	+++		ML	+	+	In other sections, IB in IF areas were scanty
	LN – 12.83	F & D, LNC	±	+		++	±	+++		ML	±	+	
2	Thyroid	F & D, LNC	±	–		+++	+++	±		A(K-, L-)	±	+	
3	Thyroid	F, LNC	+	–		±	+++	±		AL	±	+	In satellite LN, pattern was F & D
4	LN – 12.80	F, Mixed	–	–	LC with PC features	++	±	–	LC with PC features	MK	+++	+	Signet ring cells, mostly in IF areas
	LN – 2.85	F & D, LNC	–	–		+++	+++	+	Atypical large cells (?LC)	MK	+	+	Also polyclonal mature PC present
5	Eyelid	F, Mixed	++	–	SC with PC features	±	+++	–		MK	±	+	
6	LN	F, SC	+	–	SC with PC features	+	+++	–		MK & GK	±	+	Proteinaceous material in Fs Foreign body reaction in IF Biclonal gammopathy in serum

LN = lymph node; F = follicular; ML = malignant lymphoma; SC = small cleaved cells; F&D = follicular and diffuse; LNC = large noncleaved cells; PC = plasma cells; IB = immunoblasts; LC = large cleaved cells; FCC = follicular center cells; IF = interfollicular; Fs = follicles

Of the two patients with localized disease, one (#2) received combination chemotherapy and radiotherapy, the other (#3) underwent near total thyroidectomy and mantle radiation therapy, both with complete remission. These two patients are alive and well 48 and 31 months, respectively, from the presentation of their lymphoma.

Of the four patients with disseminated lymphoma, one (#5) did not receive specific treatment initially. At recurrence, one year after the diagnosis, his disease was disseminated and resulted in death, 19 months after its presentation as eyelid masses. It is relevant to add, however, that 17 months and 3 months prior to these, the patient had manifested enlargement of paraparotid lymph nodes. These lesions, neither of which is available for review, were diagnosed, respectively, as "lymphocytic lymphoma, nodular type, well differentiated" and "suggestive of lymphoma" and were not treated. All other patients with disseminated lymphoma at presentation were treated with chemotherapy. Patient #6 underwent complete remission with Leukeran and prednisone and is alive and well 19 months after presentation. Patient #4 had multiple recurrences, but is still alive with disease at 60 months. Patient #1 died with recurrent lymphoma at 61 months from presentation.

Histological and immunohistochemical findings

The lymphomas in all six patients were characterized by the presence of a follicular (nodular) component and a very marked interfollicular infiltration of plasma cells and/or their precursors. However, there was considerable histological variation among these cases, justifying somewhat detailed separate descriptions (see Table 2).

In case #1 some of the available sections showed a conspicuous follicular pattern (Fig. 1a), with nodules predominantly composed of small cleaved cells (centroblastic/centrocytic (Cb/Cc) lymphoma). Only a few large cells with abundant basophilic cytoplasm and large nucleus centered by a prominent nucleolus (immunoblasts) were observed in the interfollicular areas. In most of the sections, these cells predominated, filling the interfollicular areas (Fig. 1b) and obliterating the nodular architecture. Many immunoblasts were recognizable within the nodules (Fig. 1b). The dual cell composition, i.e. small cleaved cells and immunoblasts, was highlighted by the PAS staining, in which strong PAS-positivity marked the immunoblasts selectively. Several of the large cells featured intracytoplasmic or intranuclear inclusions, mostly eosinophilic and PAS-positive, rarely in the form of optically clear vacuoles. Few mature plasma cells were seen in this tumour. Sections from a recurrence ($4^1/_2$ years later) showed a lymphoma, follicular and diffuse, this time predominantly large noncleaved cell in type (Cb/Cc), with immunoblasts still abundant in the interfollicular areas and within the nodules.

Cases #2 and 3 were both follicular lymphomas of predominantly large noncleaved cell type (Cb/Cc), with large bands of sclerosis (Fig. 2a). Case #2 also showed extensive areas with diffuse pattern. Mature plasma cells

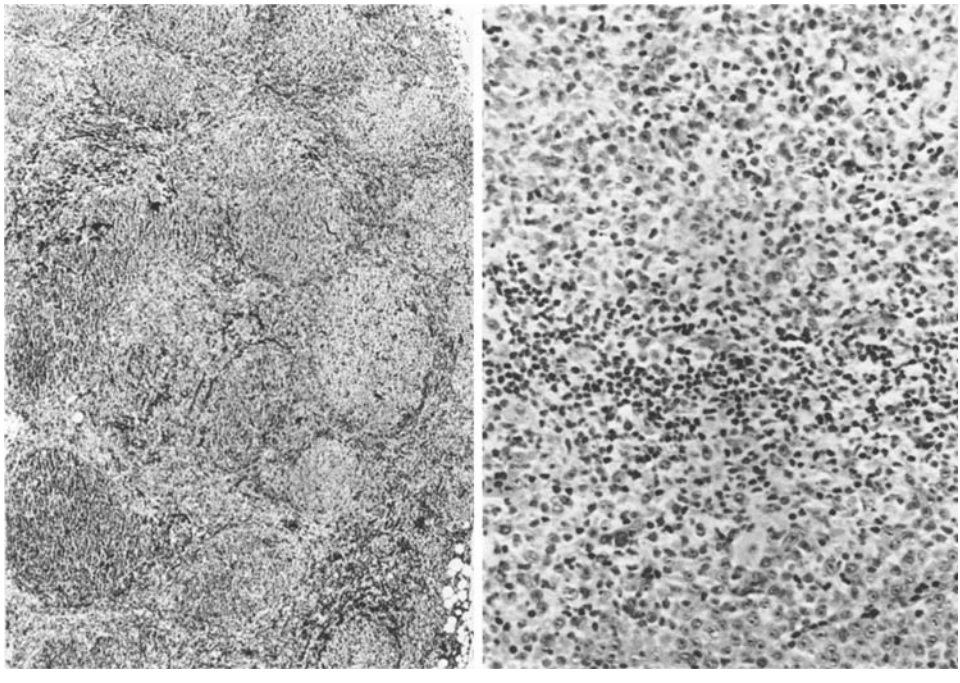

Fig. 1. Case #1. **a** Follicular pattern of the tumour. Reticulin staining (×25). **b** Immunoblasts filling the interfollicular area (*lower half*) and scattered within a nodule (*upper half*). Hematoxylin-eosin (×160)

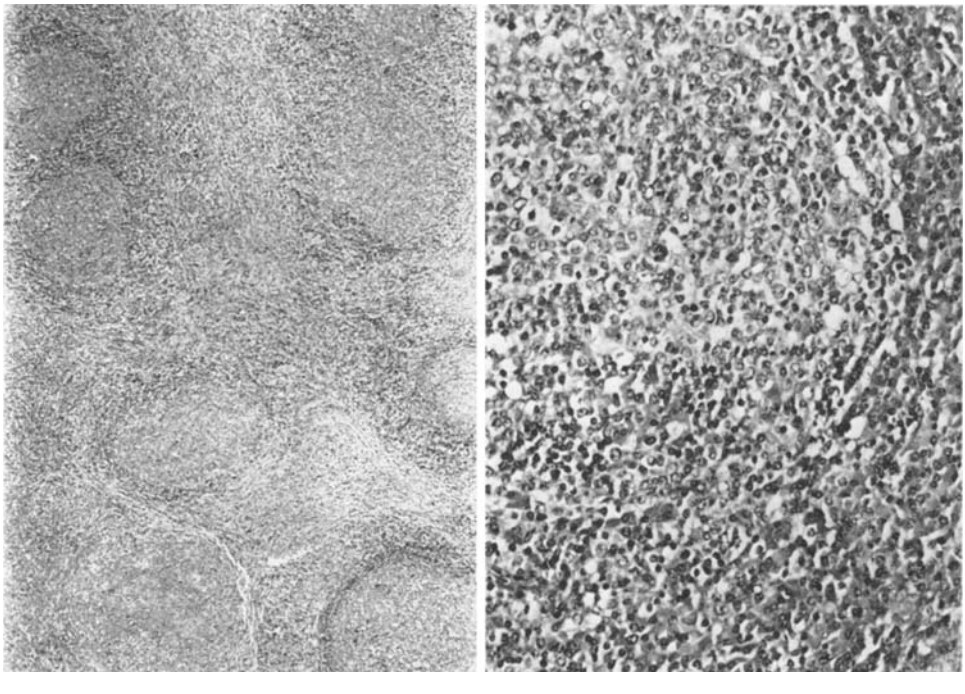

Fig. 2. Case #3. **a** Follicular pattern of the tumour, with sclerosis. Hematoxylin-eosin (×25). **b** Nodule (*left upper corner*) surrounded by plasma cells. Hematoxylin-eosin (×160)

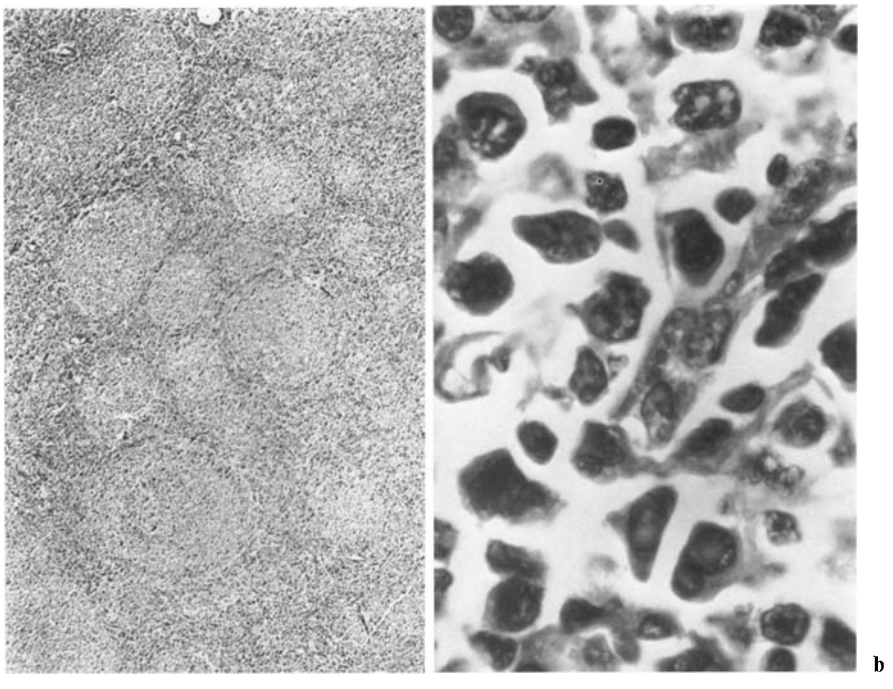

Fig. 3. Case #4. **a** Follicular pattern of the tumour. PAS (×25). **b** Cells with cleaved nuclei and plasmacytoid cytoplasm. Some contain intranuclear inclusions. Hematoxylin-eosin (×1000)

were abundant between the nodules (Fig. 2b) and in the diffuse areas, but were less common in the neoplastic follicles. Rare immunoblasts and rare intranuclear or intracytoplasmic PAS-positive inclusions were seen in both cases.

Case #4 showed somewhat different features in lymph node biopsies obtained at different times. In a 1980 biopsy the pattern was obviously follicular (Fig. 3a). The nodules had a mixed cellular composition (Cb/Cc), including a minority of large noncleaved cells and a predominant component of cleaved cells of varying size, many of which featured an abundant, homogeneous, amphohilic cytoplasm (Fig. 3b). Several of the large cells contained single or multiple inclusions. While the distortion produced by the inclusions rendered difficult a precise cytological categorization, it appeared that most cells with inclusions, by virtue of their nuclear irregularities, were cleaved cells (Fig. 3b). Similar cells infiltrated abundantly the interfollicular areas, intermixed with sparse plasma cells. In a 1984 biopsy, the pattern was follicular and diffuse and the cytology predominantly large noncleaved (Cb/Cc). Atypical large cells with abundant cytoplasm were present between the neoplastic follicles and in the diffuse areas. Some of them had large very irregular, sometimes multiple, open nuclei and small nucleoli (large cleaved cells?), but most had round or oval nuclei and, for the most part, prominent central nucleoli (immunoblasts). Inclusions were frequent in both cell types. Among these, very abundant mature plasma cells were present. It is interesting

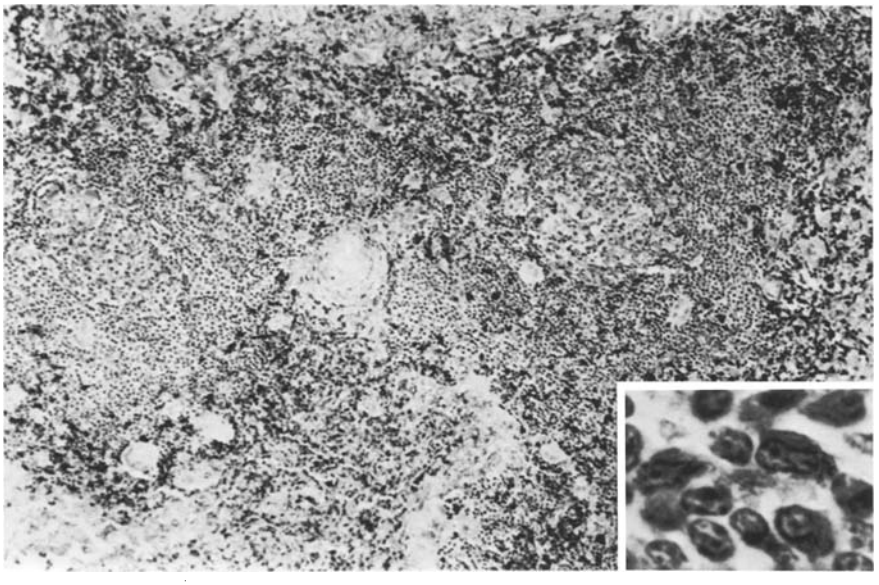

Fig. 4. Case #6. Neoplastic follicles, with intervening plasma cells and granulomatous giant cell reaction. Immunoperoxidase for IgM (×76). (*Inset*) Small cells with angulated, cleaved nuclei and plasmacytoid cytoplasm. Immunoperoxidase for IgM (×1000)

that in this patient a biopsy taken in 1983, during the interval between the two samples described above, showed a diffuse lymphoma, predominantly large noncleaved cell (Cb/Cc), with fine diffuse trabecular fibrosis. While an occasional inclusion was present in the neoplastic cells, there was otherwise no evidence of plasmacytoid features in them nor any plasma cell component to this lesion.

Cases #5 and 6 had follicular pattern (Fig. 4), one with a mixed cell and the other with a predominantly small cleaved cell composition (both Cb/Cc). Mature plasma cells heavily infiltrated the interfollicular areas (Fig. 4) and could be seen within the follicles, most frequently in case #5. In addition, in both locations, rare small cells were present that had plasmacytoid cytoplasm but cleaved nuclei (Fig. 4, inset). Features unique to case #6 were the abundance of intensely eosinophilic and PAS-positive proteinaceous deposits in most of the neoplastic follicles and the presence of a marked giant cell granulomatous reaction of foreign body type in the interfollicular areas (Fig. 4).

The immunohistochemical findings are summarized in Table 2. The cell population showing plasmacytic differentiation manifested a monotypic staining pattern for CIg in all patients. In five cases, there was exclusive reaction with either anti-K (#4, 5 and 6) or anti-L (#1 and 3) antisera. In the remaining case (#2), the neoplastic plasma cells did not stain for either light chain (even though sparse mature plasma cells reacted with both antisera), nor for any heavy chain, except IgA (Fig. 5).

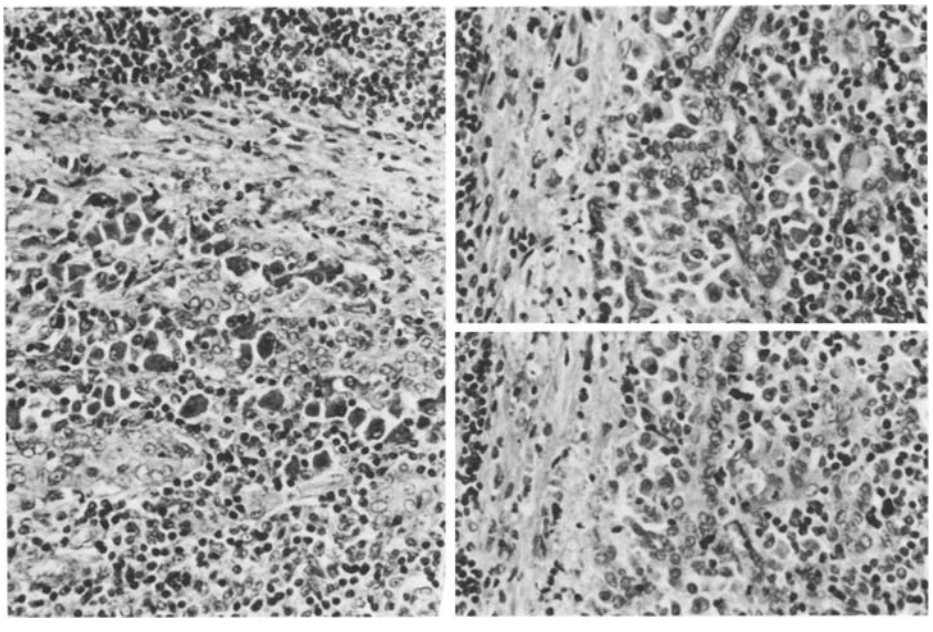

Fig. 5. Case #2. Plasma cells in serial sections stained for IgA (*left*), K (*upper right*) and L (*lower right*). Immunoperoxidase (×192)

The neoplastic plasma cell population expressed IgA in one additional case and IgM in three cases. In one instance (#6) a similar proportion of cells stained for IgM as for IgG (all of them being reactive only for K light chain). This pattern of reaction well corresponded to the biclonal peak observed in the serum immunoelectrophoresis. It is interesting to note that, while IgMK cells were present in both the neoplastic follicles and the interfollicular areas, IgGK cells (heavy chain switch) could be observed only outside the follicles.

In the two patients (#1 and 4) in whom consecutive biopsies were obtained as far apart from each other as 55 and 38 months, respectively, the monotypic staining pattern remained the same in all biopsies (IgML and IgMK, respectively). In the latter patient, the 1984 tumour, in addition to the monoclonal IgMK atypical large cells and mature plasma cells seen in the 1980 tumour (Fig. 6a), showed an abundant population of typical mature plasma cells positive for L light chain (Fig. 6b). The intracytoplasmic or intranuclear inclusions duplicated the monotypic staining pattern seen in the neoplastic cells of each case. However, staining was weak and limited to the peripheral rim of the inclusion.

In the neoplastic follicles reactivity for cIg was limited to plasma cells or to cells with plasmacytoid features, such as large immunoblasts (case #1) or atypical cells with cleaved nuclei (cases #4, 5 and 6). Positive cells in this location were relatively frequent only in cases #1, 4 and 5.

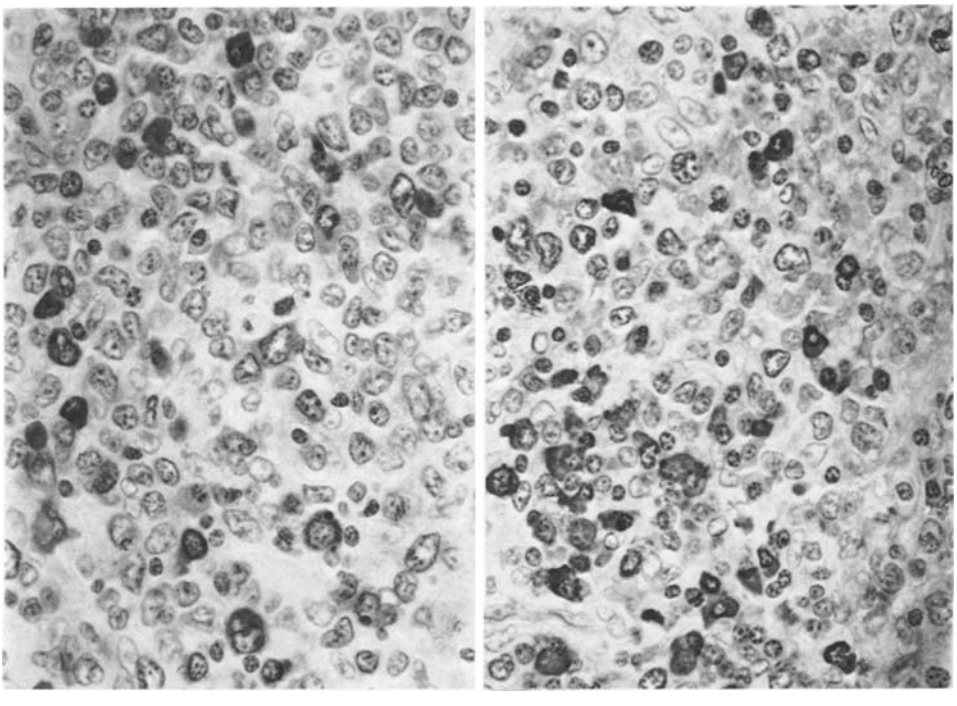

Fig. 6. Case #4. **a** Atypical large cells and plasma cells, stained for K. Immunoperoxidase (×400). **b** Typical plasma cells are positive for L, while atypical cells are negative. Immunoperoxidase (×400)

Discussion

The six tumours described here were all characterized by two components, a follicular lymphoma and a monoclonal plasma cell population. Rare instances of such association, originally mentioned by Lennert and Mohri (1978), have been reported by Nemes et al. (1981); Schmid et al. (1984) and Vago et al. (1985). A series of seven such cases has been published by Keith et al. (1985), which represented 3.5% of the lymphomas with a follicular pattern reviewed by these authors.

In all the 16 cases so far reported in detail, including ours, the monoclonal nature of the plasma cell proliferation was proven by a monotypic staining pattern in immunoperoxidase reactions for cIg. The heavy chain most often involved was IgM (69%), followed by IgA (25%) and IgG (6%). It is worthy of note that in two cases (our #2 and Nemes et al.) only A heavy chains were evident in the neoplastic cells and that all four tumours with IgA component, but only three of 12 with all other heavy chains, had extranodal presentation. Our case #6 is distinctive in that it showed an immunologically biclonal plasma cell population.

The monoclonality of the follicular center cell (FCC) component was proven in four cases of Keith et al. (1985) and in that of Vago et al. (1985)

by its immunoperoxidase or immunofluorescence monotypic reactivity. As the FCC population and the plasma cell population showed identical isotypic marking, these authors could convincingly argue the concept of plasmacytic differentiation of follicular lymphomas. In the other reported cases, due to the specific limitations of the immunoperoxidase technique, the histogenetic relationship between the two populations cannot be conclusively demonstrated, since FCC usually do not show cytoplasmic marking in paraffin sections. In these cases one cannot exclude the alternative explanation, i.e. the coexistence of two unrelated morphological types of lymphoma, composed of different clones, a phenomenon well documented in the literature (Wolfe and Borowitz 1984).

However, the concept of plasmacytic differentiation of follicular lymphoma has been favored by all the authors that have described such association, based on the presence within the follicles of plasma cells or plasmacytoid cells that manifest the same isotypic cytoplasmic marking as similar elements in the interfollicular areas, a feature also present in all of ours cases. This concept, we believe, is also supported by the presence of cell forms morphologically intermediate between FCC and true plasma cells. Such intermediate forms have been alluded to by Keith et al., and have been discussed in detail by Lennert and Mohri (1978) and Schmid et al. (1985). We detected them in three of our cases, as small cells with cleaved nuclei and plasmacytoid cytoplasm (#5 and 6) or as large atypical cells with irregular, cleaved, often multilobated nuclei and open chromatin, exhibiting a large amount of cytoplasm (#4). In both cell types the cytoplasm stained strongly for cIg.

In actual fact, morphological diversity among our six cases can best be explained by the two possible sequences of development from FCC to plasma cells proposed in principle by Lennert and Mohri (1978) (pp. 35 and 38). Case #1 showed abundant evidence of immunoblasts in the neoplastic follicles (as well as outside them), exemplifying the possibility that plasma cells derive from centroblasts (large noncleaved cells) via immunoblasts. This same sequence could explain the features of cases #2 and 3 in which centroblasts, rare immunoblasts and plasma cells were the only cell components of the tumour. By contrast, cases #5 and 6, that showed centrocytes (small cleaved cells) with cIg, and case #4, manifesting large blastic centrocytes in an early biopsy, and, later, also immunoblasts, might well represent the second possible route to plasma cells, i.e. via centrocytes transforming into blast cells. The existence of this second sequence of development is supported by recent experimental work of Braziel et al. (1985). These authors, in the successful attempt to induce in vitro immunoglobulin secretion in follicular lymphoma, observed neoplastic cells which, despite "an increased amount of cytoplasm and abundant cytoplasmic Ig", "did not develop a true plasmacytic appearance". These cells, by virtue of the nuclear features illustrated, are consistent with plasmacytoid centrocytes.

Follicular tumours with plasmacytic differentiation, therefore, appear to recapitulate the normal B-cell development to plasma cells (Vago et al. 1985). This is in contrast to the situation in the usual follicular lymphomas,

in which the FCC appear to be frozen at a non-secretory stage. The reasons for this block in differentiation are unclear and could be an intrinsic defect of the malignant FCC, immunoregulatory mechanisms in the host, or both (Braziel et al. 1985). If neoplastic FCC were intrinsically defective, one would need to explain their undisturbed differentiation in our and similar cases. If, instead, immunoregulatory mechanisms were responsible for the block in differentiation of follicular lymphomas, then our cases could be the result of alterations of such mechanisms. This second alternative may prove to be valid, based on the findings of Braziel et al. (1985), who were able to overcome such a block in vitro and induce Ig secretion by follicular lymphomas by removing autologous T-cells and providing allogeneic normal T-cells and TPA. An additional finding perhaps favoring this second alternative is the lack of morphological consistency manifested by the tumours under discussion. In Vago's et al. case, plasma cells were associated with neoplastic FCC in the nodes, but not in the bone marrow; in our case #1, follicular tumours taken years apart, showed the same monoclonal plasma cell population, but different FCC composition (small cleaved cells versus large noncleaved); and in our case #4, the definite plasmacytoid differentiation seen in the 1980 and 1984 biopsies was absent in the intervening 1983 biopsy. These findings do not fit well the concept that the neoplastic differentiation in these cases is driven by intrinsic characteristics of the tumour cell type. They would be better explained if neoplastic differentiation depended on host immunoregulatory mechanisms, which could vary at different times and sites in the same patient. Finally, the frequent presence of a prominent polyclonal plasma cell reaction, in association with the neoplastic plasma cells (our case #4; Schmid et al. 1985; Keith et al. 1985; Vago et al. 1985), also suggests that the plasmacytic differentiation in these cases is driven by host factors. It has, in fact, recently become apparent that many lymphomas not only bear close phenotypic resemblance to specific normal cell types, but also retain similar responsiveness to the same immunoregulatory influences (Ford et al. 1985).

The follicular tumours with plasma cell component under discussion are morphologically different from those described in the literature as "signet ring cell lymphoma" (Kim et al. 1978). These two types of tumours have been contrasted (Schmid et al. 1985; Keith et al. 1985; Vago et al. 1985), as Ig production is expressed in the latter by large accumulations of Ig, but not by plasmacytic differentiation. However, intranuclear or intracytoplasmic Ig inclusions were present in all of our cases and in most of Keith's et al. and, in our case #4, there seemed to occur a transition from a predominance of signet ring cells with rare plasma cells, in the 1980 biopsy, to a predominance of immunoblasts and plasma cells with less frequent inclusions, in the 1984 biopsy. Conversely, abundant plasma cells or plasmacytoid features have been described in some cases of signet ring cell lymphoma (Lennert et al. 1975; van den Tweel et al. 1978). It appears likely, therefore, that these two types of tumours, follicular with plasmacytic differentiation and signet ring cell, represent a spectrum of morphological manifestations of one biological phenomenon, i.e. the evolution of FCC towards

Ig production. Additional factors, such as aberrations of surface or internal membrane recycling, as proposed by Grogan et al. (1985), might explain the differences between the two.

The position of the follicular lymphomas with plasmacytic differentiation in our current classification schemes is unclear (Stein 1978; Vago et al. 1985; Schmid et al. 1985): with the follicular lymphomas, with the lymphoplasmacytoid tumours, or in a separate category of either type. This would depend largely on the biological behavior of this tumour, which, at this point, cannot be determined conclusively from the small number of cases reported. Available clinical information indicates a median survival of 3 years and mortality of 22%, findings that are very similar to those reported by the Kiel Lymphoma Study Group (Heinz et al. 1981) for the lymphoplasmacytic/lymphoplasmacytoid (LP) immunocytoma (33 months median survival; 30% mortality). It is interesting that seven of 16 cases reported (44%) had extranodal presentation (3 gastro-intestinal tract; 2 thyroid; 1 lung; 1 eyelid), that a high proportion (four of nine) presented with localized disease (stage I–II), and that six of 12 patients in whom serum Ig studies were performed manifested a monoclonal gammopathy. These features are not characteristic of follicular lymphomas in which extranodal involvement and localized disease at presentation are rare (14% and 20%, respectively – Goffinet et al. 1977) and monoclonal gammopathies are detected in only 0.6% of the patients, an incidence similar to that of the normal population (Braziel et al. 1985). Vice versa, extranodal presentation and serum paraproteins are quite common in LP immunocytoma (Lennert 1981; Harris and Bhan 1985).

In conclusion, the available data seem to indicate that the biological behavior of follicular lymphomas with plasmacytic differentiation is largely dictated by the plasma cell component. This might offer some ground to consider this composite tumour as a separate category from the usual follicular lymphomas, for which terms such as "follicular immunocytoma" or "follicular plasmacytoma" are perhaps appropriate.

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