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Intracellular J chains in lymphoproliferative diseases

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Summary. The presence of J or joining chains has been studied in formol-paraffin tissue sections from various lymphoproliferative diseases. The percentages of J chain positivity in 56 cases of multiple myeloma, in 41 of immunocytic malignant lymphoma and 35 of immunoblastic malignant lymphoma were 58.9, 70.7 and 37.1%, respectively. The ratio of κ to λ chain types of the monotypic Ig-s was the lowest in multiple myeloma, intermediate in immunocytic and highest in immunoblastic malignant lymphoma (ml). In 8 cases (one local immature plasmocytoma, one non-secretory multiple myeloma, one immunocytic, 4 immunoblastic and one centroblastic malignant lymphoma), only J chains were present in the tumour cells – "J chain disease". A significant difference in survival of J chain positive (26.8 months) and negative (17.7 months) multiple myeloma cases was observed. Myeloma kidney lesions were slightly more frequent in J chain negative cases. In lymphoproliferative disease J chain seems to be associated with early events of Ig synthesis. On the other hand, in two cases with biclonal Ig-s, the IgM positive immunoblastic ml cells and inclusions and the IgA positive multiple myeloma cells and inclusions were J chain positive. The IgG positive cells in both tumours and the IgG positive inclusions in the immunoblastic tumour were negative for J chains.

Key words: J chain – Immunoglobulins – Multiple myeloma – B-cell malignant lymphoma

It was Halpern and Koshland (1970) and Mestecky et al. (1971) who first described the joining on J chain, a cysteine-rich glycopeptide, present in polymeric IgA and IgM molecules and assumed to initiate polymerization of monomeric IgA and IgM. Several reports have described, however, the presence of J chains in cells containing IgG, heavy or light chains only or monomeric Ig-s. J chain has even been found in cells devoid of Ig-s

(Crago et al. 1983; Mosman et al. 1978, Mestecky et al. 1983, Reitamo et al. 1983), indicating that J chains – besides joining monomeric Ig-s – may have other functions. One of these may be the stable binding of the secretory component (part of the poly Ig receptor) to secretory Ig-s (Brandtzaeg 1974, 1976 and 1983), the others are still assumptions (Mestecky et al. 1983).

A number of studies have dealt with the occurrence of J chains in human lymphoporiferative diseases (Brandtzaeg and Berdal 1975, Isaacson and Wright 1979; Isaacson 1979, Mestecky et al. 1980; Pangalis et al. 1981; Yasuda et al. 1980; Laurent et al. 1981; Bast et al. 1981). It has become clear that (1) the J chain is usually absent in mature plasma cells, especially of the IgG isotype, its presence being a sign of immaturity of immunoglobulin (Ig)-producing cells ("early clone", Brandtzaeg 1974, Brandtzaeg and Berdal 1975), (2) as a rule, cells with ingested Ig-s – histiocytes, macrophages, Sternberg-Reed and related cells – do not contain J chains and (3) immature B-cell malignant lymphomas (ml) without any immunohistochemically detectable Ig-s may be J chain positive, the "J chain disease" of Mason and Stein 1981.

Our studies of more then 600 cases of various lymphoproliferative diseases for the presence of J chains support the above contentions. In addition, a few further observations indicate that the demonstration of J chains, besides that of Ig-s, is a further valuable diagnostic aid in this group of diseases.

Material and methods

In our studies routine formol-fixed and paraffin-embedded tissue samples from cases between 1982–83 on the files of the Department of Pathology and of the Reference Centre for Malignant Lymphomas (Kelényi and Várbiró 1980) were used. Altogether 7 local plasmocytomas, 56 multiple myelomas, 41 immunocytic, 35 immunoblastic malignant lymphomas (ml-s), 126 follicular tumours (centroblastic-centrocytic, centrocytic and centroblastic ml-s), 14 cases of angioimmunoblastic lymphadenopathy (lymphogranulomatosis X) and further reactive processes with a polytypic light chain pattern were investigated. For better immunohistological results biopsy material received in a fresh state was fixed in the second year of the study in 4% formaldehyde solution containing 5% acetic acid (Curran et al. 1982). The low pH may expose buried J chain determinants (Brandtzaeg 1983). In cases negative for J chains prolonged trypsin digestion (0.1%, pH 7.8) according to Hajdú (1983) was used.

Antisera: unlabelled rabbit antihuman Ig (κ, λ, μ, γ, α, δ) antisera, swine peroxidase-labelled anti-rabbit antisera and the PAP-complex were purchased from Dakopatts (Copenhagen) and rabbit antihuman J chain antiserum from Nordic (Tilburg). Before application of the first antiserum the deparaffinized sections were treated with undiluted swine serum for 30 min.

Either the indirect method, as described previously (Balázs and Kelényi 1980), or the unlabelled antibody method with the PAP-complex was used. The anti-J chain antiserum was diluted between 1:30 and 1:40. Since our material came from different laboratories and circumstances of fixation and embedding were not always known, those cases in which we did not see positive cells of any kind (reactive or ml cells, tested for heavy and light chains, or J chain) were excluded from the study as "technically inadequate cases". For comparison of the presence and location of the various Ig heavy and light chain and J chain positive cells, numbered serial sections were studied. In all cases routine sections stained with HE, Giemsa, PAS and reticulin were available, as were the most important clinical and immunochemical data of the cases. Statistical analysis of survivals were performed using the Mann-Whitney Rank Sum Test implemented on a Hewlett-Packard 9810A table calculator.

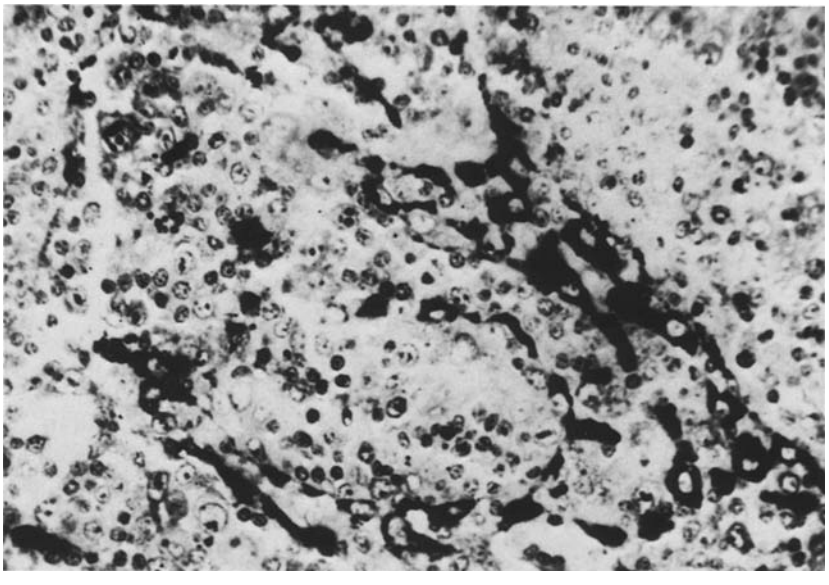

Fig. 1. Lymph node, J chain reaction, Giemsa. Strongly positive, elongated cells along the borders of and in the sinusoids. The same cells give positive reactions for κ and λ light chains and for alpha-1-antichymotrypsin. ×260

Results

In reactive processes where mature, IgG containing plasma cells predominate, the J chain reaction was usually weak or absent. Macrophages and histiocytes positive for both light chains were J chain negative. However, in two cases with a number of elongated cells probably sinus histiocytes or endothelial cells strongly positive for alfa-l-antichymotrypsin and containing both light chains, there was a positive reaction for the J chain (Fig. 1). A similar finding was described in "intrasinusoidal reticulum cells" by Curran et al. (1981). If it is assumed that the Ig-s inside these cells are phagocytosed, this phenomenon represents an exception to the rule that cells with ingested Ig-s are J chain negative (Isaacson and Wright 1979).

Angioimmunoblastic lymphadenopathy (lymphogranulomatosis X, lgX): In the 14 cases studied, the plasmocytoid cells in 7 cases were mainly strongly positive for J chain, irrespective of the predominant type of heavy chain, i.e., even if the IgG positive cells were in the majority. This finding was not related to the prognosis. In one case foci of polytypic plasma cells were seen in the usual histopathological setting of lgX; however, larger fields of plasmoblasts and immunoblasts were also present, positive only for J chains. The patient, a 75-yr-old male, died 3 weeks after biopsy at his home and additional studies were not possible.

Local plasmocytoma. Seven biopsy cases were studied (average age 52.8 years, 6 males and one female), 3 of them were vertebral tumours and

Table 1. Multiple myeloma (56 cases)

Type[a]	κ+, J+	κ+, J−	λ+, J+	λ+, J−	Only J+	Total
Plasmocytic	2	1	4	3	–	10
Mixed type	3	3	1	4	1	12
Plasmoblastic	10	4	7[b]	3	–	24
Giant cell or anaplastic	3	3 (+1)[c]	2	2	–	10
Total	18	11	14	12	1	56

[a] See Wutke et al. 1981
[b] IgD myeloma case in this group
[c] One biclonal case, IgA/κ/J positive and IgG/κ/J negative

the others tumours of the tonsil, epipharynx, stomach and duodenum. At the time of diagnosis the bone marrow did not show any plasma cell infiltration. Three of the cases were negative and four positive for J chains. Of special interest was a tumour of the duodenum the cells of which contained neihter heavy nor light chains, but J chains only. This tumour was fairly immature, built up in part of plasmoblastic-immunoblastic cells. Of the 6 other cases 3 were of κ and 3 of the λ type, the heavy chain (known in 4 cases) was IgG in 2 and IgA also in 2 of the 4 cases. The 2 IgG and one of the IgA positive cases expressed J chains.

Multiple myeloma. A total of 56 cases were studied. In 17 of them bone marrow tissue particles from biopsy material alone were available, in 18 autopsy tissues alone and in 21 both were available. Twenty-five of the cases were males and 21 females, their average age being 62.0 and 64.8 years, respectively. Table 1 shows that in 33 cases (58.9%) the myeloma cells were positive for J chain. The intensity of the reaction varied greatly, and in one and the same tissue clusters of positive and negative cells were seen in agreement with the observations of Yasuda et al. (1981).

Positive and negative cases were nearly equally distributed between cases with monotypic IgG and IgA or with monotypic κ and λ light chain. The J chain positive cases were most frequent in the plasmoblastic type (17 positive and 7 negative cases). The occurrence of "myeloma kidney", i.e., massive impacted casts surrounded by granulation tissue (31 cases studied in autopsy material) was higher in the J chain negative (7 from 11) than in the positive (6 from 20) cases. Survival in the patients of the two groups was nearly the same (average 24.4 and 22.6 months). It should be pointed out, however, that in 8 cases the diagnosis of myeloma multiplex was established either at autopsy or only a few weeks before death, survival after the first complaints being 1–3 months. If these cases, one with and 7 without massive casts are excluded, the survival of the cases with the renal lesion is significantly shorter (26.4 vs. 36.9 months). The survival of the 22 patients with J chain positive cells was 26.8 months, of the 14 patients without J chain 17.7 months, this difference was significant ($p < 0.01$).

In one case of non-secretory myeloma (survival 36 months) the myeloma

Table 2. Malignant lymphoma, immunocytic (41 cases)

Type	κ+, J+	κ+, J−	λ+, J+	λ+, J−	Only J+	Total
Plasma cell	1	–	1	–	–	2
Lymphoplasmocytoid	4	4	2	1	1	12
Lymphoplasmocytic	10	1	4	1	–	16
Polymorphous	6	4	–	1	–	11
Total	21[a]	9	7[a]	3	1[a]	41

[a] J chain positive: 29 cases (70.7%)

cells contained only J chains. In another case (giant cell or anaplastic type, with biclonal gammopathy) the more immature myeloma cell line was IgA/κ/J chain positive with a large number of PAS and J chain positive Dutcher bodies, the other less numerous cell type was IgG/κ/J chain negative. In these cells no inclusions were seen (Fig. 2). A case of IgD/λ myeloma (plasmoblastic type, survival 36 months) was J chain positive as expected on the basis of observations of Brandtzaeg et al. (1979).

It is known that in the course of the disease, the type of myeloma cells may change to a more immature type (Wutke et al. 1981). In 2 such cases there was no change in the presence or absence of J chains, when studied in biopsy and in autopsy material. In our material we did not find cases of the monotypic light chain type (4 cases were not tested for intracellular heavy chains).

Malignant lymphoma, immunocytic. Altogether 41 cases (in 1 autopsy, in 33 biopsy tissues and in 7 both were available) were studied, 19 males and 22 females, their average ages being 65.2 and 66.0 years, respectively. 27 of the patients had nodal tumours, 14 extranodal (stomach 6, orbit 2, intestines, testicle, lung, larynx and palatum, one case each). In the extranodal group the lymphoplasmocytic and polymorphous types, i.e. ml-s of follicular or possibly follicular origin (Stein et al. 1981; Lennert 1978) predominated (11 out of 14 cases). The findings are shown in Table 2. 29 cases (70.7%) were positive for J chains, in one only J chains were seen (Fig. 3). This case with only J chains was a 29-yr-old female who is alive 23 months after diagnosis (splenectomy). In this group of ml-s there was, in contrast to multiple myeloma, a predominance of κ light chain type cases. In 18 cases the monotypic heavy chain was known from our immunohistological data (13 IgM and 5 IgG). The ratio of J chain positive/negative cases was evenly distributed with the light chain type.

J chain positivity predominated in lymphoplasmocytic tumours. Since the majority of extranodal ml-s were of this latter type, it is conceivable that these tumours were as a rule J chain positive (11 positive out of 14).

In 7 cases PAS-positive Russell and Dutcher bodies were seen in high numbers and in 3 more cases their number was smaller, all 10 were IgM/κ/J chain positive. The J chain reaction of the Dutcher bodies was frequently stronger than the cytoplasmic reaction of neighbouring plasmocytoid cells

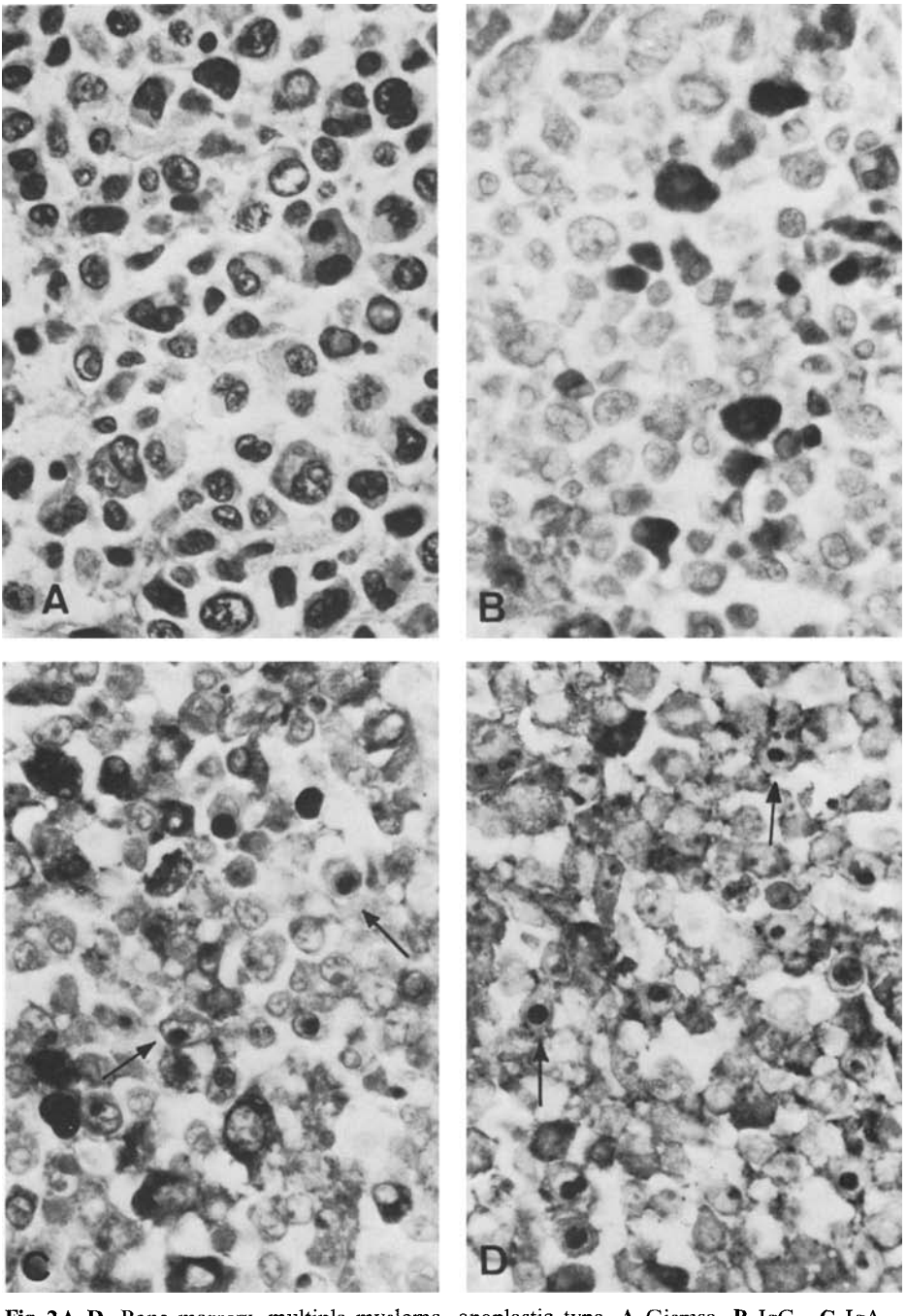

Fig. 2A–D. Bone marrow, multiple myeloma, anaplastic type. **A** Giemsa, **B** IgG-, **C** IgA-, **D** J chain-reaction. In **C–D** Dutcher bodies (intranuclear inclusions, *arrows*), but not in **B**. ×560

or of the Russell bodies (Fig. 4). In tumours with only Russell bodies 6 were positive and 3 negative for J chains.

Malignant lymphoma, immunoblastic. 35 cases were studied, in 23 biopsy, in 9 biopsy and autopsy and in 3 only autopsy tissues were available. There were 17 males and 18 females, their average age being 64.9 and 68.2 years, respectively. The survival (known in 13 cases) was 5.3 months. 19 tumours were nodal and 16 extranodal (stomach 9, tonsils, skin, brain each 2, epipharynx 1). Immunohistologically 18 were monotypic κ and 2 λ positive, 7 and 2 among these positive for J chains. In 4 cases the tumour cells contained only J chains and in 12, although a few positive plasma cells were seen, the tumour cells were negative for heavy, light and J chains. Altogether 13 cases (37.1%), 8 nodal and 5 extranodal, were J chain positive.

Two of the nodal cases with only J chains showed a high number of positive cells, in the other two cases (one of them a nodal and the other a brain tumour) scattered groups consisting of a few positive cells were seen. In a stomach immunoblastic ml the predominant IgM/κ cells and few Dutcher bodies displayed J chain positivity. Besides, however, PAS positive Russell bodies were also observed, they were IgG/κ positive, but negative for J chains.

Malignant lymphomas of follicular origin. (*A*). 37 centroblastic-centrocytic and 10 centrocytic ml-s were studied for light chains and J chain. 6 centroblastic-centrocytic and 2 centrocytic ml-s showed a monotypic pattern (5 κ, one λ and one κ, one λ positive), two of each group were J chain positive. Out of 94 centroblastic ml-s 72 were investigated for light chains and J chain. 4 monotypic cases were seen, 3 κ/J chain positive, one λ/J chain negative. In a further case only J chains were present in larger groups of immature blasts (61-years-old-man, generalized lymphadenomegaly at the time of diagnosis).

(*B.*) *Centroblastic-centrocytic ml with α-heavy chain disease:* Two cases were studied, a 57-year-old man with an ileocoecal and a 21-year-old man with a tonsillar lymphoma. Both were of follicular structure and the plasmocytoid cells, both in the follicles and in their vicinity displayed α-heavy chain and J chain positivity, but were negative for light chains. Many Dutcher bodies were seen both positive for α-heavy and J chain. Serum immunoelectrophoresis gave negative results for monoclonal Ig-s and there was no Bence-Jones proteinuria. These cases were similar to those described by Isaacson et al. (1983) among malignant lymphomas from the Middle East, by Asselah et al. (1983) from Algeria and to the case of Nemes et al. (1981) in Hungary.

(*C.*) *Signet ring cell lymphomas* are follicular tumours containing monotypic intracytoplasmic Ig-s. We have seen 5 such cases, 3 corresponding to type I of Navas-Palacios et al. (1983), one to type II, in the fifth PAS positive crystalline inclusions were inside the cisternae of rough endoplasmic reticu-

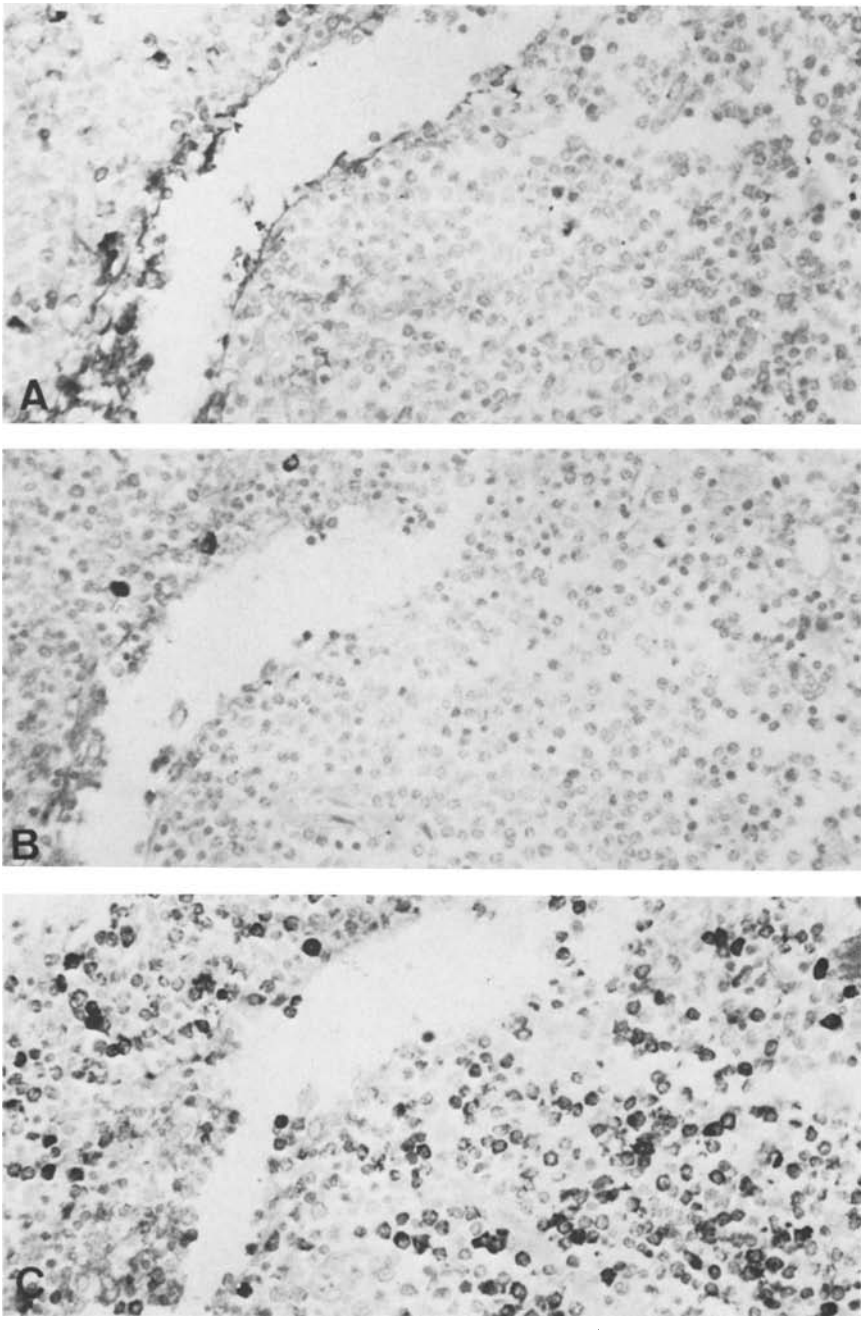

Fig. 3A–C. Splenic hilar lymph node, immunocytic malignant lymphoma, adjacent sections. **A, B** κ and λ light chain, **C** J chain-reaction, Giemsa. × 260

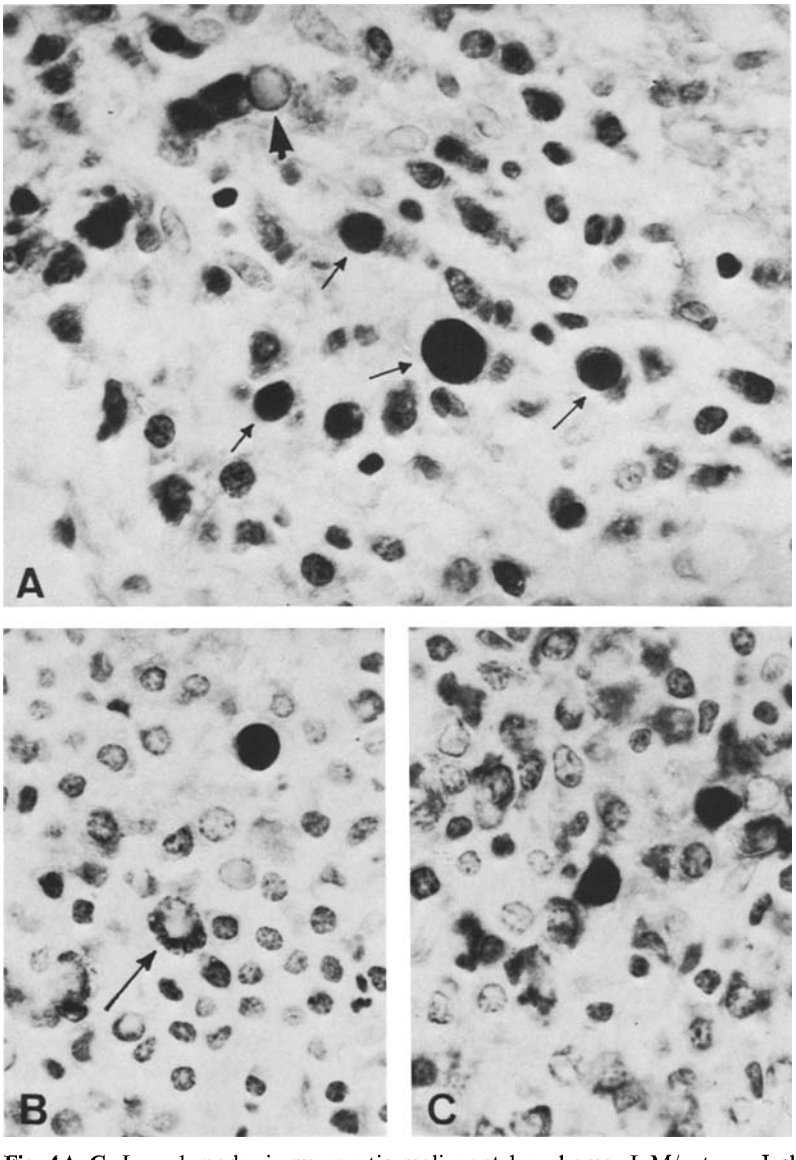

Fig. 4A–C. Lymph node, immunocytic malignant lymphoma, IgM/κ type, J chain-reaction. **A** Several J chain positive (*arrows*) and one negative (*arrowhead*) Dutcher body. **B** One Dutcher body and a cell with globular cytoplasmic inclusions (Russell body, *arrow*), **C** two Dutcher bodies and plasmocytoid cells positive for J chains. × 690

lum. The 3 cases of type I were of the IgG/κ type, 2 J chain positive, one negative. The case of type II did not contain either heavy, light or J chains. The case with the cristalline inclusions was positive for IgG/κ and negative for J chains.

Discussion

In the course of differentiation of lymphocytes the earliest sign of their commitment to the B lineage is the rearrangement of the immunoglobulin (Ig) genes from their germline configuration to a functionally active stage. The first Ig to appear is intracytoplasmic μ heavy chain in pre-B cells, followed by the surface Ig-s and at the terminal stages of differentiation cytoplasmic Ig-s are synthetized and secreted with a switch from IgM and IgD to IgG, IgA or IgE.

The genetic regulation of J chain synthesis is not known, there are, however, observations indicating that, although not present in surface Ig-s (Brandtzaeg 1976; Raschke et al. 1979; Kutteh et al. 1982), it may appear at early stages of lymphocyte differentiation, or it even may preceed the synthesis of cytoplasmic Ig-s (McCune et al. 1981; Mather et al. 1981; Benjamin et al. 1982; Hajdu et al. 1983).

Malignant lymphomas corresponding to more advanced phases of lymphocyte differentiation have been studied by several groups (Brandtzaeg and Berdal 1975; Isaacson and Wright 1979; Isaacson 1979; Mestecky et al. 1980; Yasuda et al. 1980; Laurent et al. 1981; Bast et al. 1981; Pangalis et al. 1981). In these tumours the frequency of J chain expression might be influenced besides other factors by three circumstances (1) by the anaplastic nature of the cells, (2) by the fact that ml and multiple myeloma cells synthetizing polymeric IgM or IgA should – according to our present knowledge – exhibit J chain positivity and (3) by the immaturity of the tumour cells being in early stages of B-lymphocyte differentiation.

Let us consider these points in detail:

(1) The low number of J chain positive cases in the group of immunoblastomas (37.1%) and their more frequent occurrence in multiple myelomas and immunocytic lymphomas (58.9 and 70.7%) may be explained by the more anaplastic nature of the first group. It should be mentioned that Laurent et al. (1981) have seen J chain positivity in only 2 out of 39 cases of immunoblastomas.

(2) Our findings in immunocytic lymphomas (IgM type, 11 positive, one negative, IgG type, 2 positive, 3 negative) do support to some extent the contention outlined in (2) above. Furthermore, in an anaplastic myeloma and in an immunoblastic lymphoma we have seen biclonal Ig-s, the IgA positive cells and inclusions in one and the IgM positive cells and inclusions in the other, were J chain positive. The IgG positive cells in both cases and the IgG positive inclusions in the immunoblastic tumour were J chain negative. This seems to be a further proof of the isotype dependence of J chain positivity. In multiple myeloma our findings do not support the idea of Ig isotype dependence of J chain expression.

The high number of J chain positive immunocytic lymphomas of extranodal localisation (11 out of 14) might be related to the presence at some of these sites of a predominant although not exclusive presence of gland associated plasma cells, in which J chain enables the complexing of the

secretory component to the polymeric Ig-s (Brandtzaeg 1974, 1976 and 1983). These cells are functionally more immature than IgG cells in chronic inflammation (Yasuda et al. 1981). This might also explain the frequent J chain positivity in Middle Eastern intestinal lymphomas (Isaacson et al. 1983) as in two cases of α-heavy chain disease of the present study, although in similar tumours α-heavy chains are as a rule not polymeric (Mestecky et al. 1977).

(3) Since μ and κ chains are the first heavy and light chains synthetized in the course of B-cell differentiation, the increasing predominance of κ light chain types from multiple myelomas (29 out of 55) to immunocytic (29 out of 39) and to immunoblastic ml-s (18 out of 20) is not surprising and seems to be in accordance with our present knowledge of lymphocyte-plasma cell differentiation. It may also be assumed that immunocytic ml-s represent an earlier stage of lymphocyte differentiation than multiple myeloma, with the predominant monoclonal isotypes in the first being IgM or IgG, in the second IgG or IgA. The high percentage of J chain positive cases in the IgM type ml-s as well as in the plasmoblastic type of myeloma cases might indicate that J chain expression is an early event in the process of Ig synthesis.

In those cases in which only Russell bodies were seen, there was a predominance with monotypic IgG and 8 out of 13 were J chain positive. In contrast, simultaneously occurring PAS-positive Dutcher and Russell bodies were of the IgM/κ isotype and all were J chain positive. Inclusions in Ig-synthetizing lymphomas developing in the course of Sjögren's disease were found to be predominantly in the IgM/κ type and J chain positive (Schmid et al. 1982). Since Dutcher bodies are possibly inclusions developing at the perinuclear cisternae of rough endoplasmic reticulum and are thus signs of an early phase of Ig synthesis, their frequent association with J chain is a further argument for the involvement of J chains in the initial phases of Ig synthesis.

The findings of McCune et al. (1981); Mather et al. (1981); Benjamin et al. (1982) and Hajdu et al. (1983) that J chain expression may preceed Ig synthesis is corroborated by the occurrence of malignant lymphomas whose cells contain only J chains ("J chain disease" of Mason and Stein 1981), although the absence of Ig synthesis may be a sign of cellular anaplasia. The fact that 5 of the present 8 such cases, as those 3 of Mason and Stein (1981) and the one of Möller et al. (1982) were ml-s of high grade malignancy further supports the view that J chain synthesis is linked with early stages of Ig production and assembly. It is worth like to mention that in IgM cells of secretory tissues there is an excess of free cytoplasmic J chains (Brandtzaeg 1983) and that in murine plasmocytomas there might be J chain production in excess in IgM positive cells (Parkhouse et al. 1976), or only J chain synthesis (Mosman et al. 1978), situations reminiscent of "J chain disease".

In *multiple myeloma* our studies showed nearly identical percentages of J chain positive cases (58.9%) to those of Yasuda et al. (1980); Mestecky et al. (1980), (Laurent et al. (1981), but fewer then in the work of Bast

et al. (1981). Our data indicate that the presence of J chains is, besides others (Acute Leukemia Group B, Cooperative Study 1975), an additional feature of the monotypic Ig-s, which shows some correlation with the frequency of myeloma kidney lesions and especially with the prognosis of the patient.

In immunocytic and signet ring cell ml-s Russell and Dutcher bodies were positive for a given monotypic heavy and light chain, and were PAS positive. In multiple myeloma Blom et al. (1976) found that Russell bodies are PAS negative and reactive for only light chains. The causes of these differences in the characteristics of the inclusions are not clear.

Although we did not study Russell bodies of myeloma cells in detail, in a few cases they were found to be PAS positive and containing also heavy chains. However, our findings agree with those of Blom and Wiik (1983) and Mepham and Wright (1983) that the inclusions contain Ig-s. The presence of J chains besides Ig-s in Russell and Dutcher bodies speaks in favour of their view and against the opinion of Hsu et al. (1982) that Russell bodies are free of Ig-s.

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