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Angioimmunoblastic Lymphadenopathy

Histopathology of Bone Marrow Involvement*

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Summary. 23 cases of angioimmunoblastic lymphadenopathy (AILAP) diagnosed by lymph node biopsy were investigated with regard to bone marrow involvement, using plastic embedding technique. 14 patients (61%) out of 23 displayed a granuloma-like focal or extended infiltrate, predominantly in the center of the bone marrow spaces. This lesion contained lymphocytes, plasma cells, histiocytic reticulum cells and sometimes immunoblasts with whorls of arborizing vessels and increased reticulin fibers. The different types of cellular infiltration in lymph nodes in AILAP are not encountered in bone marrow. Further, there is only a relatively slight increase of vessels which are not always as thick-walled in the bone marrow as in the lymph nodes of AILAP patients. 7 out of 14 (50%) cases with marrow involvement died with recurring lymphomas and infiltration of liver and spleen after 4 to 54 months after the first biopsy. This demonstrates the unfavorable clinical outcome of AILAP with bone marrow infiltration, since only 2 of 9 patients (22%) without marrow involvement at the time of biopsy have died to date: one had toxic heart failure following chemotherapy and another developed septicaemia. Early marrow lesions of Hodgkin's disease and granulomas in hyperergic myelitis of rheumatic origin have a very similar appearance and may therefore be confused with AILAP infiltrates. Histopathology of lymph nodes is therefore an essential requirement in differentiating between these disorders. The outstanding value of bone marrow biopsy in AILAP-patients is firstly, in staging the disease and secondly, in early recognition of systemic spread connected with an unfavorable prognosis.

Key words: Angioimmunoblastic lymphadenopathy – Bone marrow involvement – Histopathology – Differential diagnosis – Prognosis.

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Introduction

In the past 10 years angioimmunoblastic lymphadenopathy (AILAP) has been regarded as a relatively rare and systemic immunoproliferative disease. It is characterized by a variable clinical outcome and an abnormal number of T- and/or B-cells, and considered to be due to various stimuli like medicaments or viral infection (Lukes and Tindle 1975; Frizzera et al. 1975; Radaszkiewicz and Lennert 1975; Nathwani et al. 1978; Lennert et al. 1979). The histopathology of AILAP is well documented and described in these reports. However, Lennert and his coworkers (1979) extended those morphological findings and regarded the disease as pre-lymphoma, while introducing a novel classification which depends on cellular composition. These reports on AILAP describe involvement in lymph nodes, but there are only relatively few cases recorded in the literature in which bone marrow infiltrates are described (larger series: Lukes and Tindle 1975; Pangalis et al. 1978; Nathwani et al. 1978).

The question whether AILAP represents a systemic disorder may be answered by the investigation of bone marrow. Of further interest is the prognosis of patients with systemic spread of the disease by comparison with those cases displaying lymph node infiltrates only. We also intend to compare the findings in the bone marrow with the histopathology of AILAP in lymph nodes and to see if there is a characteristic pattern of marrow involvement.

Patients and Methods

Since 1975 we have investigated a total of 40 patients with AILAP; 23 of these cases had a core biopsy of the anterior or posterior iliac crest, in a few sequential examinations were performed. The trephine biopsies were performed following the techniques of Jamshidi and Swaim (1971) or Burkhardt (1966), specimens were fixed in Schaffer's solution and embedded in methyl-methacrylate (further details see Vykoupil et al. 1976). Routine staining methods included Giemsa, Goldner's trichrome, silver impregnation after Gomori, Prussian blue reaction, periodic-acid-Schiff (PAS) and methyl-green-pyronin (MP). This study comprises only patients who displayed AILAP in lymph nodes.

Results

An overview with basic data of our 23 patients with AILAP in lymph nodes who underwent core biopsies of the bone marrow is given in Table 1. 14 out of 23 cases (61%) revealed focal or extended granulomatous infiltrates of the bone marrow (Table 2). Among the remaining 9 patients 7 displayed a non-specific so called hyperergic or inflammatory reaction of the marrow with peri-capillary plasmacytosis, an oedematous swelling of the vessel walls and also a patchy oedema of the myeloid stroma. Many necrobiotic neutrophilic granulocytes were seen with phagocytosis by histocytic reticulum cells. There was proliferation of granulopoiesis with a moderate shift to the left. Increased iron storage was found. One case showed a reactive hyperplasia of haematopoiesis and another a normal specimen.

Table 1. Basic data of our patients with AILAP in lymph nodes and bone marrow biopsies ($n=40$)

	Number of patients	Mean age (years)	Sex ratio M = male F = female
Lymph nodes involved	40	50	23 M/17 F
Bone marrow investigated	23	52	13 M/10 F
Bone marrow involved	14	57	9 M/ 5 F
Bone marrow not involved	9	46	4 M/ 5 F

Table 2. Bone marrow involvement in patients with AILAP proven by histopathology of lymph nodes

Patients initials	Age	Sex	Pattern of involvement	Deceased after biopsy	Alive (months)	Recurrent lymphomas
1. B.C.	51	M	f	27		+
2. F.H.	36	M	e	24		+
3. G.A.	64	F	f		48	−
4. G.A.	76	M	f		2	−
5. J.R.	62	M	f	10		+
6. K.E.	73	M	f		4	−
7. M.H.	69	M	f		14	−
8. R.S.	41	M	e	54		+
9. K.E.	55	F	e		40	n.a.
10. W.B.	37	M	e		17	n.a.
11. B.B.	84	F	f	4		+
12. S.W.	67	M	[a]	12		Hodgkin lymphoma[a]
13. D.H.	65	F	f+e	12		+
14. T.G.	24	F	f		29	−

M = male, F = female, f = focal, e = extended, n.a. = not available

[a] Autopsy revealed Hodgkin's disease with extended infiltration and fibrosis of the bone marrow (Duhamel et al. 1971)

Clinical findings demonstrated that the mean age of the cases with bone marrow involvement was higher than that of patients without infiltrates (Table 1). The follow-up covered a period between 4 and 54 months. 7 (50%) of our 14 patients with bone marrow involvement died within 4 to 54 months after the first biopsy (Table 2). 6 patients that died showed finally a massive recurrence of AILAP with developing lymphomas and infiltration of the liver and – partially – the spleen. The last of these patients died of respiratory insufficiency due to infiltration of the lungs by AILAP.

In contrast to these findings 7 out of the 9 patients (88%) who had no involvement of the bone marrow at the time of biopsy are still alive. The remaining 2 died of septicaemia and toxic heart failure following chemotherapy. With regard to the problem of malignant transformation of AILAP, 4 of our patients developed malignant lymphomas, 3 of the immunoblastic type and one Hodgkin's disease. Another patient had Hodgkin's disease 8 years ago

and lymph node biopsy now revealed AILAP. In 3 of these cases no core biopsy was performed. The patient with Hodgkin's disease had a negative bone marrow biopsy but autopsy revealed extended infiltration by Hodgkin's lymphoma. One of the cases with immunoblastic lymphoma disclosed extended granulomatous infiltration by AILAP in the trephine biopsy.

Histopathology of AILAP in the bone marrow revealed two different patterns of infiltration. The majority of our cases exhibited a focal type of granulomatous infiltrate, mostly in the center of the marrow spaces; only in 2 out of 14 cores there were granulomas with a close association to the osseous trabecula (Fig. 1a). The second pattern was characterized by an extended granulomatous involvement, frequently extending over the whole specimen (Fig. 1b). Transition between these patterns was also to be seen, but the cellular composition of these two types of infiltrates disclosed no differences. The granuloma-like infiltration showed a varying amount of lymphocytes, plasma cells and histiocytic cells, scattered around prominent vessels and with proteinaceous flocculent oedema (Fig. 2a). In 3 cases a particularly remarkable insterstitial material was observed consisting of patchy scleroedema with finely fibrillar structures associated with a granuloma (Fig. 2b, 4a). Most cases exhibited immunoblasts with large nuclei and one or more prominent nucleoli and pyroninophilic cytoplasm (Fig. 2c). No giant cells were to be seen. A striking architectural detail of these granulomas – whether extended or focal – was the apparently increased vascularization by capillaries and postcapillary venules together with the whorl-like arranged reticulin fibers (Fig. 2a, 3a, b). Prominent thickening of capillary basement membrane was only rarely detected and was accompanied by a remarkable perivascular plasmacytosis (Fig. 3a, b compare with Fig. 3c). The increase of reticulin fibers – as shown in silver impregnation – corroborated the granuloma-like character of involvement and demonstrated the arborizing capillaries (Fig. 3a, b, d). In contrast with the histopathology of lymph nodes there was no such different cellular composition in the marrow infiltrates. In addition the prominent vascularization observed in lymph nodes was not as conspicuous in the bone marrow specimens and interstitial material was less frequently encountered in marrow biopsies. Furthermore, the remarkable thickening of vessel walls was not obvious in marrow infiltrates.

One of our patients (case 12, Table 2) with AILAP in lymph node had no involvement of the bone marrow at the time of the first marrow biopsy. However, he died 12 months later and autopsy revealed Hodgkin's disease in most lymph nodes and extensive fibrosis without Hodgkin or Reed-Sternberg cells in the bone marrow. The remaining 5 cases, with sequential trephines, displayed identical patterns of infiltration except for one (case 13, Table 2), which showed a focal pattern in the first and extended involvement in the following two corings.

Discussion

Our findings demonstrate AILAP infiltration of the bone marrow in 61% of our cases (Table 3). Radaszkiewicz and Lennert (1975) found 3 out of 6 (50%)

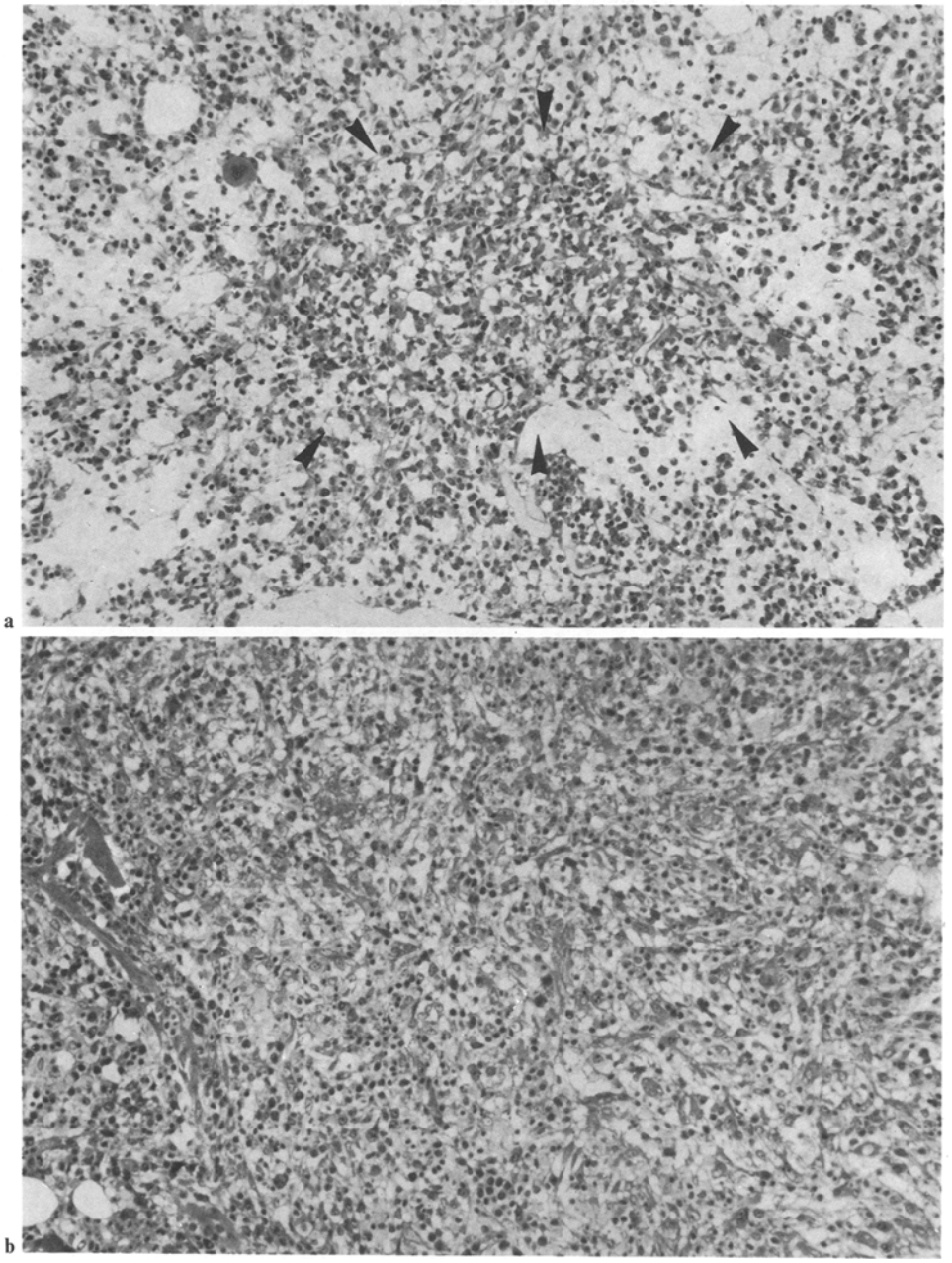


Fig. 1 a and b. Survey of bone marrow involvement by angioimmunoblastic lymphadenopathy (AILAP). **a** *Focal* infiltrate with increase of cells, reticulin fibers and vessels (*arrow heads*) with conspicuous demarcation towards the remaining marrow space. **b** *Extended* infiltration with remarkable fibrosis and increased vascularization leading to a total obliteration of normal hematopoiesis. **a** and **b** × 140

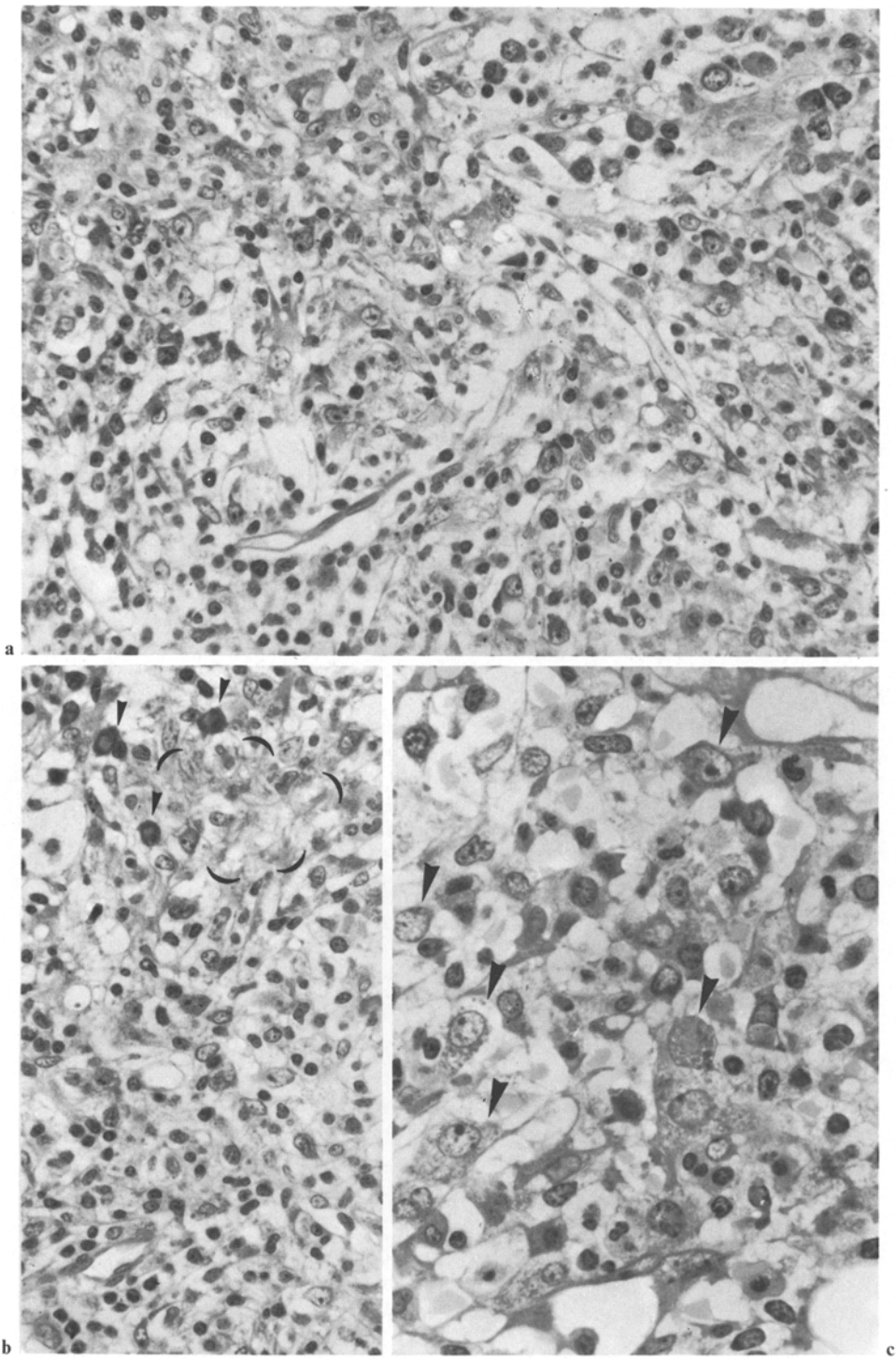


Fig. 2a–c. Cellular composition and interstitial material of AILAP infiltrates of the bone marrow. **a** Overview with lymphoplasmacytoid cells, histiocytic reticulum cells and lymphocytes surrounded by a mesh of whorl-like arranged reticulin fibers, capillaries and patchy oedema. **b** Plasma cells (*small arrow heads*) surrounding an area of scleroedema with fibrillar interstitial material (*brackets*), in the lower half many lymphocytes. **c** Several immunoblasts (*arrow heads*) interspersed between lymphocytes and histiocytic reticulum cells. **a** and **b** × 350; **c** × 560

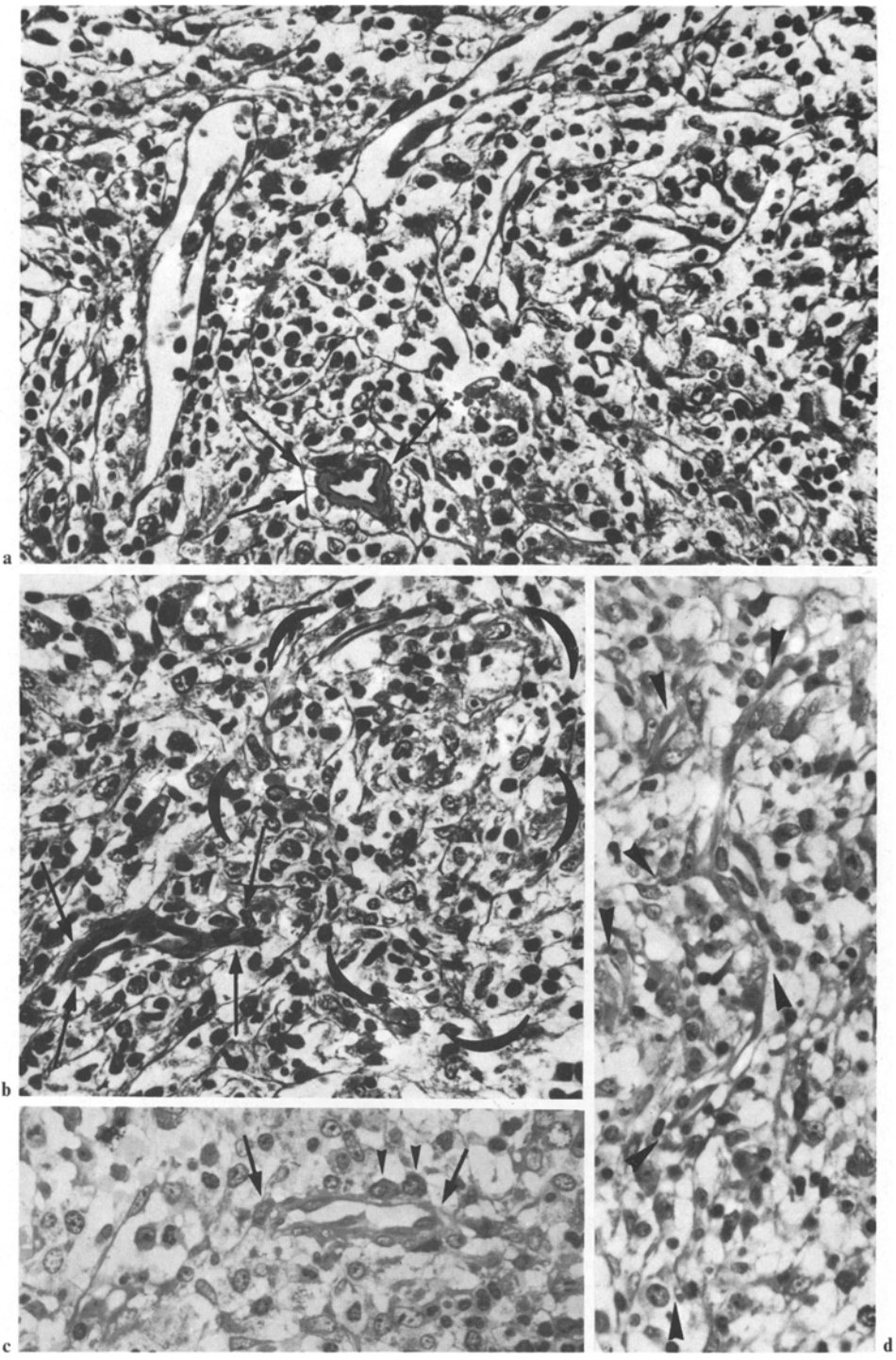
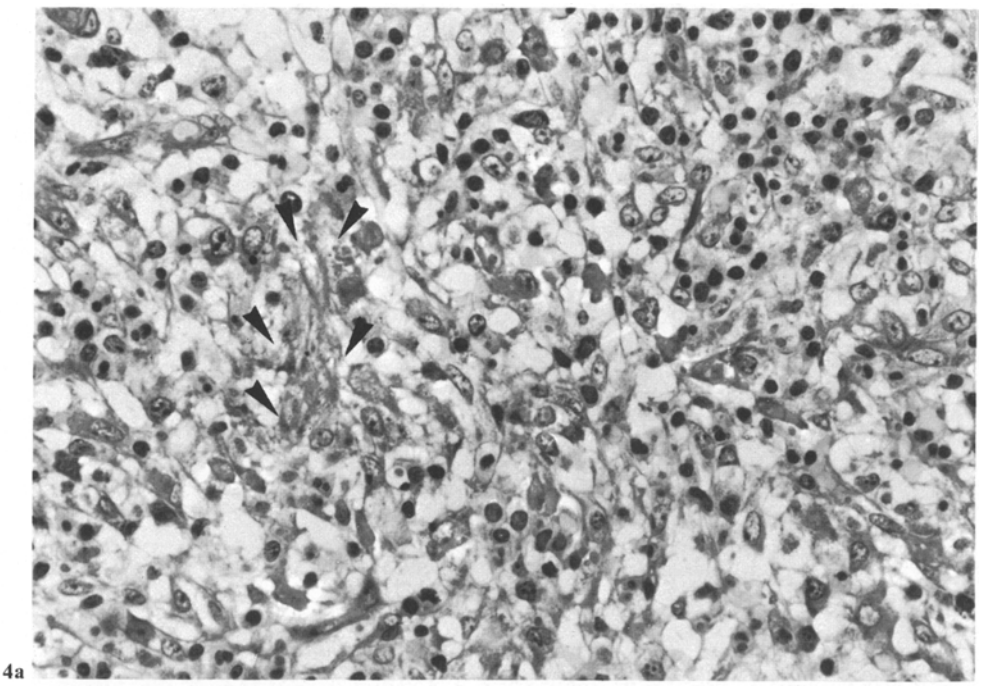
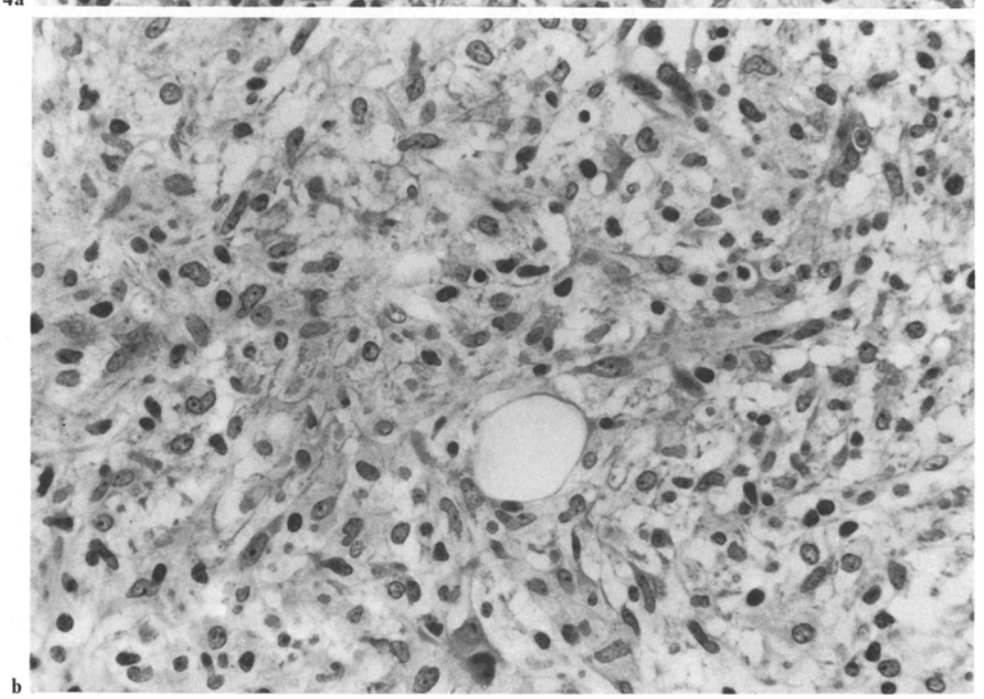


Fig. 3a–d. Reticulin fibers and vessels of AILAP infiltrates of the bone marrow. **a** General architecture of reticulin fibers and capillary vessels in *extended* infiltrate after silver impregnation (Gomori's stain). Long arrows mark a crossly sectioned capillary with a thickened wall. **b** Whorl-like or granulomatous arrangement in a focal infiltrate indicated by brackets and in close connection with a capillary showing a thickened wall (long arrows, silver impregnation after Gomori). **c** A corresponding illustration of a capillary in Giemsa's staining with broadening of the vascular wall (*arrows*) and a perivascular deployment of plasma cells (*small arrow heads*). **d** Course of an arborizing capillary vessel with branchings shown in tangential and cross sections and indicated by arrow heads. **a** and **d** × 350; **b** and **c** × 350

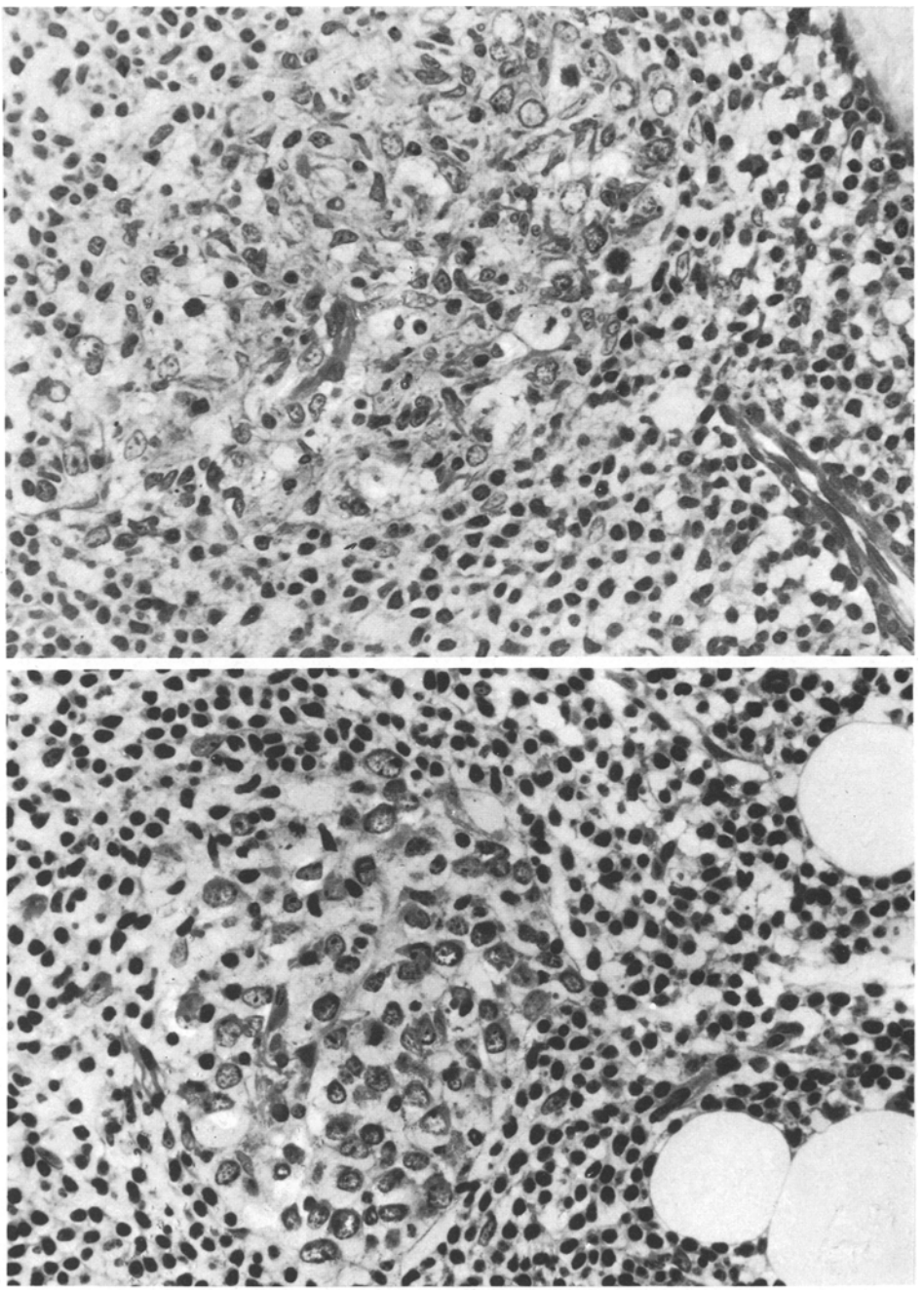


4a



b

Figs. 4a and b, and 5a and b. Differential diagnosis of AILAP-like granulomatous lesions of the bone marrow. **4a** *AILAP* infiltrate with patchy oedema (*arrow heads*) and whorl-like arrangement of histiocytic reticulum cells, lymphocytes and plasma cells besides increase of capillaries. **4b** *Hodgkin's disease* with non-specific infiltrate with a similar appearance of histiocytic cells, reticulin



5a

b

fibers and lymphoplasmacytic elements; no Hodgkin cell or giant cell of the Reed-Sternberg type visible. **5a** *Rheumatic myelitis* (PCP) with granulomatous infiltrate showing a wall of lymphocytes surrounding a focal proliferation of histiocytic cells and vessels. **5b** *Scleroderma* with generalization and focal infiltrate of the bone marrow containing many histiocytes and dispersed lymphocytes in the surroundings. **4a**, **b** and 5**a**, **b** × 350

Table 3. Bone marrow involvement of AILAP; comparison of our results with the pertinent literature

Authors	Bone marrow	
	involved	not involved
Radaszkiewicz and Lennert (1975)	3/ 6	3/ 6
Lukes and Tindle (1975)	4/10	6/10
Nathwani et al. (1978)	15/23	8/23
Pangalis et al. (1978)	19/27	8/27
Own results (1980)	14/23	9/23

bone marrow biopsies with granulomatous infiltrates, Lukes and Tindle (1975) $^{4}/_{10}$ (40%), whereas Nathwani et al. (1978) reported $^{15}/_{23}$ (65%) and Pangalis et al. (1978) $^{19}/_{27}$ (70%) cases. Thus Nathwani et al. (1978) also found more than a half of their cases displayed bone marrow involvement in biopsies. At autopsy 9 out of 22 patients revealed bone marrow involvement by AILAP and – partially – immunoblastic lymphoma and another 5 cases showed infiltrates of scattered large lymphoid cells.

Thus depending on the nature of the marrow infiltration it is obvious that AILAP may evolve into a systemic immunoproliferative disorder including the T- and B-cell compartment (Matz et al. 1977; Neimann et al. 1978; Schnaidt et al. 1979). Evaluation of our results shows that the involvement of bone marrow in AILAP suggests an unfavorable clinical prognosis: 7 out of 14 patients (50%) with bone marrow infiltration are already dead, whereas only 2 out of 9 cases (22%) of those without involvement have died. Classification of AILAP into several subtypes according to the cellular composition as in the lymph nodes (Lennert et al. 1979; Schnaidt and Thiele 1980) is not possible with bone marrow infiltrates. Since there is no evidence for conspicuous differences, not even in the elaborate and refined technique of plastic embedding and semithin sectioning, this result is very significant. The interstitial material which forms a spot-like or patchy oedema may however be comparable with features in the lymph nodes (Frizzera et al. 1975; Neiman et al. 1978; Nathwani et al. 1978; Schnaidt et al. 1980a). In contrast, the remarkable increase of vascularization and the broadening of the walls of the vessels are rarely seen in the granuloma-like lesions of the bone marrow (compare Fig. 3b with 3c). The diagnosis of AILAP based on the morphology of bone marrow without examination of a lymph node raises some problems. The diagnosis of AILAP in bone marrow is only feasible if it is confirmed by a lymph node biopsy showing its characteristic pattern of involvement. With regard to the differential diagnosis of AILAP in the bone marrow there is first and most important of all, the extended and focal pattern (Fig. 1b, 4a and 1a) with its varying vascularization and increase of histiocytic reticulum cells and reticulin fibers. This may, however, be confused with nonspecific infiltrates in Hodgkin's disease (Fig. 4b). This is because early involvement of Hodgkin's disease may have a quite similar appearance with an absence of Hodgkin cells or characteristic giant cells of the Reed-Sternberg type (Bartl et al. 1976; O'Carroll et al. 1976; Schnaidt et al. 1980b). Our finding adds an additional morphological feature to the well known

non-specific mesenchymal reaction in bone marrow in patients with Hodgkin's disease (Georgii and Vykoupil 1974; te Velde et al. 1978). A further differential diagnosis for the focal infiltrates of AILAP in the bone marrow may be a granulomatous lesion in hyperergic myelitis of rheumatic origin (Fig. 5a, b). There is a focal increase of histiocytic cells with prominent vessels and a perivascular plasmacytosis surrounded by a loose aggregation of lymphocytes, e.g. in cases with PCP (Fig. 5a). Similar difficulties may possibly arise from the presence of lymphohistiocytic granulomas with delicate small vessels, e.g. in scleroderma (Fig. 5b).

By analogy with the early and non-specific infiltrates in Hodgkin's disease, we agree with O'Carroll et al. (1976) that such a lesion of the bone marrow warrants a lymph node biopsy. This is an essential requirement, firstly to establish a correct diagnosis and, secondly to differentiate clearly Hodgkin's disease from AILAP.

A further deduction from our results can be made about prognosis (Table 2): bone marrow infiltrates in AILAP and multiple lymphomas, and the involvement of liver and spleen indicate systemic spread of this disease. Consequently there is evidence both from the pertinent literature and also from our findings, that involvement of bone marrow in AILAP implicates generalized disease and therefore an unfavorable clinical outcome.

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References

Bartl R, Burkhardt R, Lengsfeld H, Huhn D (1976) Die Bedeutung der histologischen Knochenmarksbeurteilung bei Morbus Hodgkin. Klin Wochenschr 54:1061–1075

Burkhardt R (1966) Präparative Voraussetzungen zur klinischen Histologie des menschlichen Knochenmarkes. Blut 14:30–46

Duhamel G, Najman A, André R (1971) Les localisations à la moelle osseuse de la maladie de Hodgkin! Leur place dans l'évolution de la maladie. Etudes par biopsie médullaire de 100 observations. Presse med 79:2305–2308

Frizzera G, Moran EM, Rappaport H (1975) Angio-immunoblastic lymphadenopathy. Diagnosis and clinical course. Am J Med 59:803–818

Georgii A, Vykoupil KF (1974) Unspecific mesenchymal reaction in bone marrow in patients with Hodgkin's disease. Rec Res Cancer Res 46:39–44

Jamshidi K, Swaim WR (1971) Bone marrow biopsy with unaltered architecture. A new biopsy device. J Lab Clin Med 77:335–342

Lennert K, Knecht H, Burkert M (1979) Vorstadien maligner Lymphome. Verh Dtsch Ges Path 63:170–196

Lukes RJ, Tindle BH (1975) Immunoblastic lymphadenopathy. A hyperimmune entity resembling Hodgkin's disease. N Engl J Med 292:1–8

Matz LR, Papadimitriou JM, Carroll JR, Barr AL, Dawkings RL, Jackson JM, Herrmann RP, Armstrong BK (1977) Angioimmunoblastic lymphadenopathy with dysproteinemia. Cancer 40:2152–2160

Nathwani BN, Rappaport H, Moran EM, Pangalis GA, Kim H (1978) Malignant lymphoma arising in angioimmunoblastic lymphadenopathy. Cancer 41:578–606

Neimann RS, Dervan R, Haudenschild C, Jaffe R (1978) Angioimmunoblastic lymphadenopathy. An ultrastructural and imunologic study with review of the literature. Cancer 41:507–518

O'Carroll DI, McKenna RW, Bruning RD (1976) Bone marrow manifestations of Hodgkin's disease. Cancer 38:1717–1728

Pangalis GA, Moran EM, Rappaport H (1978) Blood and bone marrow findings in angioimmunoblastic lymphadenopathy. Blood 51:71–83

Radaszkiewicz T, Lennert K (1975) Lymphogranulomatosis X. Dtsch Med Wochenschr 100:1157–1163

Schnaidt U, Krmpotic E, Stünkel K, Georgii A (1979) Angioimmunoblastische Lymphadenopathie: Ein Vorläufer des malignen Lymphoms? Verh Dtsch Ges Pathol 63:379–383

Schnaidt U, Thiele J (1980, in press) Lymphogranulomatosis X (oder Angioimmunoblastische Lymphadenopathie): Vergleich von Licht- und Elektronenmikroskopie im Lymphknoten. Verh Dtsch Ges Pathol 64

Schnaidt U, Thiele J, Georgii A (1980) Angioimmunoblastic lymphadenopathy: Fine structure of the lymph nodes by correlation of light and electron microscopical findings. Virchows Arch A Path Anat and Histol 389:381–395

Schnaidt U, Vykoupil KF, Thiele J, Scheler S, Georgii A (1980b, in press) Granulomatöse Veränderungen im Knochenmark. Verh Dtsch Ges Pathol 64

te Velde J, den Ottolander GJ, Spaander PJ, van den Berg C, Hartgrink-Groeneveld CA (1978) The bone marrow in Hodgkin's disease: the non-involved marrow. Histopathology 2:31–46

Vykoupil KF, Thiele J, Georgii A (1976) Histochemical and immunohistochemical techniques on acrylate embedded bone biopsies. Blut 32:215–218

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