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Histopathology of bone marrow in human immunodeficiency virus infection

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Summary. The clinical and haematological findings in 18 patients with human immunodeficiency virus (HIV) infection were correlated with the histological features of plastic embedded bone marrow biopsies. Fifteen patients presented with peripheral cytopaenia of one or several cell lines. Twelve (66%) of the 18 patients exhibited bone marrow findings including normo- to hypercellularity, myelodysplasia, lymphocytosis with or without plasmacytosis and fibrosis of the reticulin type. Seventeen patients had myelodysplastic features, 5 of the 3 haematopoietic lines, 10 of 2 lines and 2 of 1 line. Dysmegakaryocytopoiesis and dyserythropoiesis, seen in 88% and 83% of the 18 patients respectively, were the most common myelodysplastic features. Bone marrow gelatinous transformation (serous atrophy) was a conspicuous finding in 7 (38%) of the 18 patients. The constellation of histological features here described, although not pathognomonic, is highly suggestive of HIV infection. The pathogenesis of the haematological abnormalities in HIV infection is discussed.

Key words: Acquired immunodeficiency syndrome – HTLV-III – Bone marrow diseases – Bone marrow examination – Histological technics

Introduction

Infection by the HIV (Human Immunodeficiency Virus or HTLV III/LAV) is frequently associated with a significant cytopaenia in the peripheral blood (Morbidity and Mortality Weekly Report (MMWR) 1986). Bone marrow findings in HIV infection have been reported in several studies with diverse results (Abrams et al. 1984; Castella et al. 1985; Geller et al. 1985; Osborne et al. 1984; Schneider et al. 1985; Shenoy and Lin 1986; Spivak et al. 1984). Whereas Abrams et al. (1984) found no specific marrow abnormalities which could account for the blood cytopaenia, Geller et al. (1985) described a distinctive marrow pattern with hypercellularity and fibrosis. The frequency of mycobacterial and fungal infections and lymphoid and/or lymphomatous infiltrates in biopsy specimen have been stressed by others (Castella et al. 1985; Osborne et al. 1984). In addition, Schneider et al. (1985) pointed out myelodysplastic features in the marrow smears of patients with HIV infection.

We report histological observations of glycol methacrylate embedded bone marrow sections from 18 patients with HIV infection, as defined by the Center for Diseases Control (CDC) (MMWR 1986). In our hands, plastic embedded biopsy, without decalcification, has proved to be the best tool for analysing both quantitative and qualitative disorders of bone marrow (Delacrétaz et al. 1987).

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Material and methods

Between December 1981 and December 1986, 18 patients who met the CDC criteria for HIV infection (MMWR 1986) had a bone marrow biopsy.

Bone marrow biopsies were performed with a Jamshidi needle at the posterior iliac crest together with a marrow aspirate. Specimens were fixed in glutaraldehyde and embedded in glycol methacrylate (Sorvall R) without decalcification, according to our previously described technique (Delacrétaz et al. 1987). Sections 2 micrometer thick were stained using the following standard procedures: Giemsa, silver impregnation according to Gomori, Prussian Blue, Ziehl-Nielsen and PAS.

Marrow cellularity was considered to be normal when 30% to 75% of the surface of the marrow cavity was occupied by the haematopoietic tissue (Peel and Krause 1981). Increased number of megakaryocytes corresponded to more than 3 megakaryocytes per HPF and decreased number to less than 1

per HPF (Krause 1981). A myelo-erythroid ratio of 1.5:1 to 3:1 was considered normal according to Krause (1981). Criteria for myelodysplasia were those proposed by the FAB Group (Bennett et al. 1982). The term "myelodysplasia" is used in a descriptive sense and does not necessarily implicate a "premalignant state" (see discussion). Dyserythropoiesis: multinuclearity, nuclear fragments, cytoplasmic abnormalities, ring sideroblasts (>15%). Dysgranulopoiesis: nuclear abnormalities, hypogranular cells. Dysmegakaryocytopoiesis: micromegakaryocytes, large mononuclear forms, small nuclei, reduced number of megakaryocytes.

Plasmacytosis was diagnosed when there were more than 5% plasmacytes. Lymphocytosis was diagnosed only in the presence of lymphoid clusters. According to Bauermeister (1971), the reticulin stroma was considered normal when only rare and thin reticulin fibers were visualised by the Gomori stain. A diffuse fine fiber network with or without scattered thick fibers was interpreted as fibrosis.

Results

The clinical and haematological characteristics of the 18 patients studied are summarized in Table 1.

Two patients were female and 16 male. The mean age was 30 years (range 23 to 58 years). One patient belonged to group II of the CDC classification, 3 to group III and 14 to group IV. Four presented with a malignancy: Kaposi's sarcoma in 3 patients (No. 5, 10 and 16) and intestinal non-Hodgkin lymphoma in 1 patient (No. 18). Fifteen had lymphadenopathy and 4 splenomegaly. A lymph node biopsy was performed in 8 patients, with a diagnosis of hyperplastic lymphadenitis in 5 (No. 2, 9, 12, 14 and 16), tuberculous lymphadenitis (Mycobacterium tuberculosis hominis) in 2 (No. 7 and 15) and Kaposi's sarcoma in 1 (No. 10). A recent body weight loss of more than 10% was observed in patients No. 8, 9, 10, 12, 16 and 17. The risk factors were drug addiction in 8 patients, homosexuality in 3, drug addiction and homosexuality in 1, origin from Zaïre or Rwanda in 5 and a male partner from Zaïre for 1 woman. Seropositivity for HIV was demonstrated in the 16 patients in which the test was performed. For patients No. 10 and 16, sera were not available to be tested.

For 15 of the 18 patients, the bone marrow examination was prompted by a cytopaenia and for 3 of them by a suspicion of infection and/or lymphoma. Criteria for cytopaenia were as follows: $\leq$100 g/l Hb corresponded to anemia, $\leq$1,8 G/l neutrophiles to neutropenia, $\leq$100 G/l thrombocytes to thrombocytopenia. The haematological data are summarized in Table 1. Four patients had neutropaenia (No. 5, 10, 13 and 14), 4 thrombocytopaenia (No. 1, 2, 9 and 12), 5 neutro-thrombocytopaenia (No. 3, 4, 6, 8 and 15), 1 anaemia and thrombocytopaenia (No. 11) and 1 pancytopaenia (No. 7). Lymphopaenia ($\leq$0,8 G/l lymphocytes) was present in 10 of the 18 patients.

The immunological data were as follows: a decreased OKT 4/OKT 8 ratio was noted in the peripheral blood of 9 of the 13 patients tested; a polyclonal hypergammaglobulinaemia was present in 12 of the 16 patients tested; seven patients were

Table 1. Patient population

No	Sex age	Risk Fact.	CDC group*	Hb g/l	N G/l	T G/l	Ly G/l
1	M24	D	II	150	2,5	14	0,8
2	M25	D	III	144	2,0	12	2,9
3	M28	D	III	141	1,6	7	1,0
4	M23	D	III	128	1,6	7	1,0
5	M30	Z	IVD	138	0,3	112	1,1
6	M26	D	IVC2	150	1,3	100	0,6
7	M26	Z	IVC1C2	86	1,7	53	0,8
8	M39	H	IVAC1	104	0,6	22	0,6
9	M30	Z	IVA	152	3,6	22	0,8
10	M40	H	IVA1C1D	135	1,4	208	0,4
11	F 23	D	IVABC1C2	66	3,3	71	0,5
12	M28	R	IVAC2	115	2,3	58	1,5
13	M58	R	IVAE	122	1,1	185	1,4
14	F 25	PZ	IVA	109	0,6	114	1,2
15	M26	D+H	IVC2	152	1,3	85	0,9
16	M44	H	IVAC1D	101	2,8	156	0,7
17	M28	D	IVAC1C2	120	2,2	236	0,1
18	M23	D	IVD	143	2,9	255	0,6

Abbreviations: D = Drug addiction. H = Homosexuality; R = Origin from Rwanda; Z = from Zaïre; PZ = Partner from Zaïre; Hb = Haemoglobin; N = Neutrophils; T = Thrombocytes; Ly = Lymphocytes

* The CDC groups are detailed in MMWR (1986)

Table 2. Histopathology of the bone marrow

Patient No	CDC group**	Peripheral blood	Bone marrow findings									
			Cellularity	M/E	Mega	DysE	DysG	DysM	Plasmacytosis	Lymphoid clusters	Fibrosis	Gelat. Transf.
1	II	Thrombocytopaenia	↗	N	↗	+	0	+	0	+	+	0
2	III	Thrombocytopaenia	↗	N	↗	+	0	+	0	0	+	0
3	III	Neutrothrombocytopaenia	N	N	N	+	0	+	0	0	0	0
4	III	Neutrothrombocytopaenia	N	N	↗	0	0	+	0	0	0	0
5	IVD	Neutropaenia	N	↓	↓	+	0	+	+	0	+	0
6	IVC2	Neutrothrombocytopaenia	N	N	N	0	0	+	0	+	+	0
7	IVC1C2	Pancytopaenia	N	↓	↓	+	0	+	+	0	+*	+
8	IVAC1	Neutrothrombocytopaenia	N	N	N	+	+	+	+	0	+	+
9	IVA	Thrombocytopaenia	N	N	↗	+	+	0	0	0	0	0
10	IVA1C1D	Neutropaenia	↗	↗	↓	+	+	+	+	+	+	+
11	IVABC1C2	Anemia + Thrombocytopaenia	↗	↓	↗	+	0	+	+	+	+*	+
12	IVAC2	Thrombocytopaenia	↗	N	↗	+	0	+	+	0	+	0
13	IVAE	Neutropaenia	↗	↓	N	+	+	+	+	+	+	0
14	IVA	Neutropaenia	↗	N	↓	+	+	+	+	+	+*	0
15	IVC2	Neutrothrombocytopaenia	N	N	N	+	0	+	0	0	+	0
16	IVAC1D	No cytopaenia	N	N	N	+	+	+	+	+	+	+
17	IVAC1C2	No cytopaenia	N	N	N	+	0	+	+	+	+	+
18	IVD	No cytopaenia	↗	N	N	0	0	0	+	0	+	+

Abbreviations: M/E = myelo-erythroid ratio. Mega = number of megakaryocytes. DysE = dyserythropoiesis. DysG = dysgranulopoiesis. DysM = dysmegakaryocytopoiesis. Gelat. transf. = gelatinous transformation; N = normal

* = dry tap

** The CDC groups are detailed in MMWR (1986)

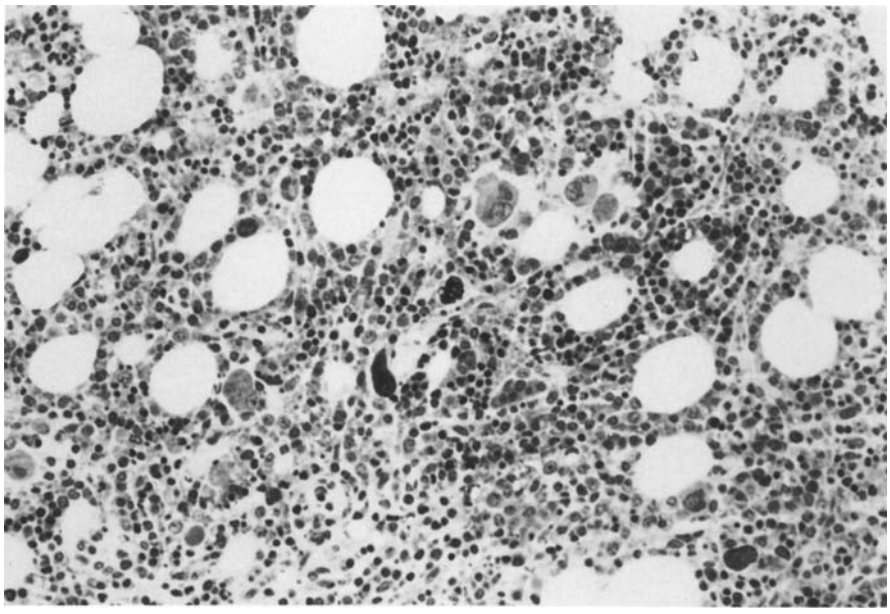


Fig. 1. Marrow hyperplasia with increased number of megakaryocytes. In some areas, the fat cells have a dissociated pattern. Giemsa ×150

found to have platelet-associated antibodies or elevated levels of immune complexes in the peripheral blood; these seven patients were thrombocytopaenic (No. 1, 2, 3, 4, 6, 9 and 11). Marrow microbiological cultures were performed in 6 of the 18 patients. They were all negative. Among the cytopaenic patients, 2 were taking drugs which may induce cytopaenia: Dipyrone (Novalgine R) (No. 12), triple antituberculous therapy with Ethambutol, Rifampicin and Isoniazid (No. 7). No patient was receiving Co-Trimoxazole at the time of the biopsy, but 2 of them (No. 8 and 10) had taken the drug 2 weeks before the biopsy for treatment of a Pneumocystis Carinii infection.

The results derived from the study of bone marrow biopsies are summarized in Table 2.

Marrow cellularity was increased in 8 (Fig. 1) and normal in 10 patients. A dissociated pattern of fat cells, as described by Geller et al. (1985) with "hematic cells separating but not effacing fat cells" was present in 4 cases with hypercellularity (No. 10, 11, 12 and 18). Patients No. 2 and 14 showed only some areas of this dissociated pattern. In patients No. 1 and 13, the hypercellularity was considered compact. The myelo-erythroid ratio was normal in 13, increased in 1 and decreased in 4 of the 18 patients. A shift to the left of the granulocytic line and an increased number of eosinophiles were seen in many cases (11 of 18). The number of megakaryocytes was found to be increased in 6 (Fig. 1), normal in 8 and decreased in 4 patients.

All patients but 1 (No. 18) displayed myelodysplasia (Fig. 2), according to the FAB criteria. Five patients had myelodysplastic features of the 3 lines, 10 of 2 lines and 2 of 1 line. Dysmegakaryocytopoiesis and dyserythropoiesis were the most frequent myelodysplastic features, seen in respectively 16 and 15 patients, whereas dysgranulopoiesis was noted in 6 patients only (Fig. 2a–d). Atypical megakaryocytes were characterized by hyposegmented or ovoid ("monocytoid") nuclei or by the presence of multiple small nuclei with occasionally degranulated cytoplasm. Megakaryocytes with naked nuclei (without cytoplasm) and micromegakaryocytes (30 micrometers and less in diameter) were also encountered. Bizarre erythroblasts with lobulated or fragmented or flower-like and double nuclei were observed. Asynchronism of nucleo-cytoplasmic maturation and/or cytoplasmic degranulation and/or pelgeroid nuclei were considered dysgranulopoietic features.

Increased number of reactive cells, plasmacytic and/or lymphocytic, was observed in most patients (13 of 18). Eleven biopsies contained more then 5% of plasma cells, 3 of them having more than 20%. In 8 of 18 specimens, clusters of lymphoid cells were found, sometimes along the bone trabeculae. The lymphoid cells were characterized by some variation in nuclear size and shape and in abundance of cytoplasm (Fig. 3). Some of them had immunoblastic or "monocytoid" appearance, resembling the "B monocytoid cells" encountered in lymphadenitis (Sohn et al. 1985). Cytomegalic inclusions were found together with a lymphoid cluster in patient No. 16 (Fig. 3). In 10 of 18 cases, an increased number of macrophages was observed. Nuclear debris and/or pigments (haemosi-

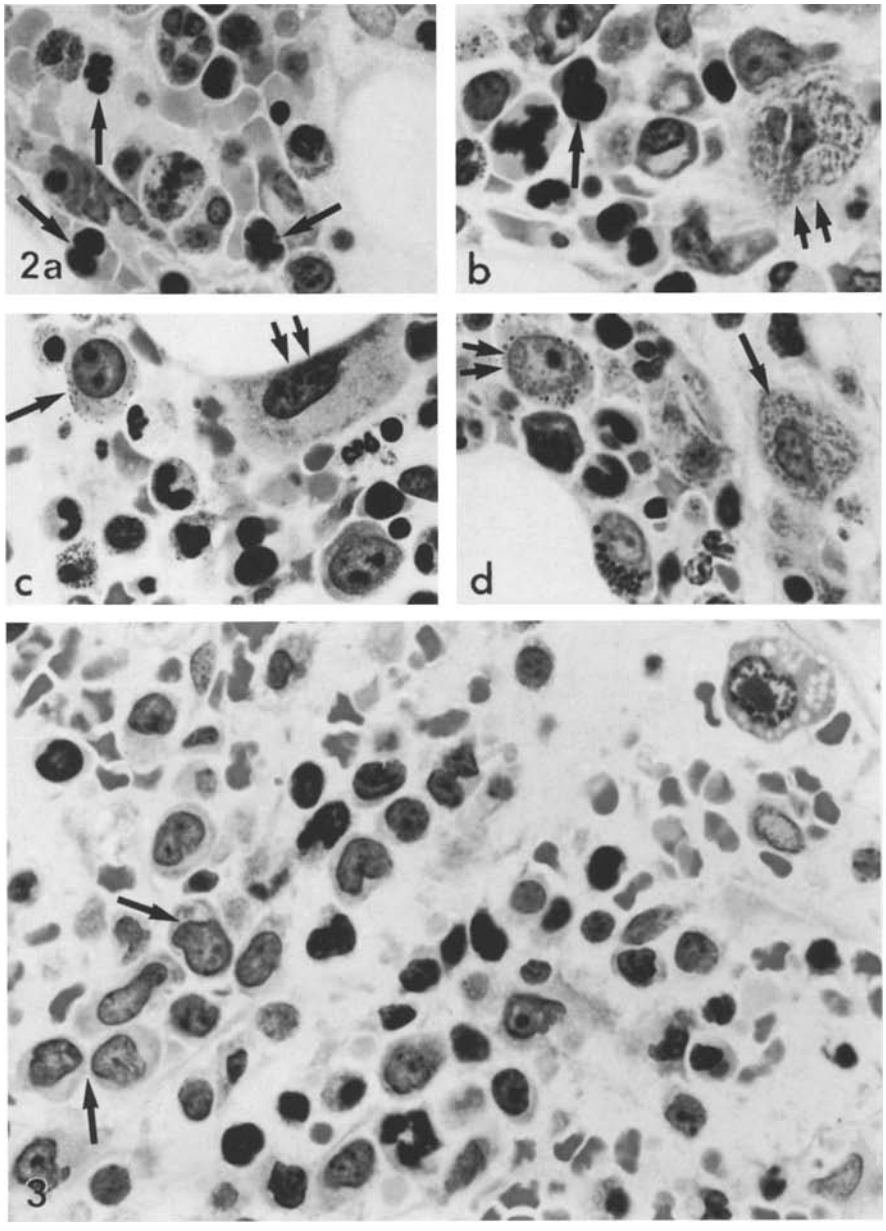
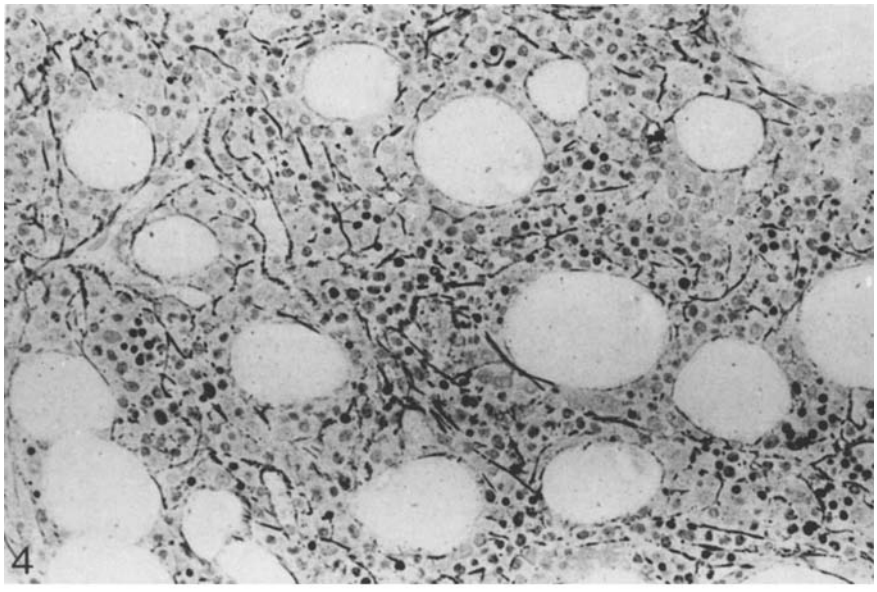


Fig. 2. Myelodysplastic features seen in HIV infection: **a** Dyserythropoiesis (↗), with multilobated or "flower-like" nuclei. **b** Dyserythropoiesis (↗) with double nucleus and atypical mitosis. Atypical megakaryocyte (↗ ↗). A plasma cell is visible in the center of the picture. **c** Dysgranulopoiesis: myelocyte with partly degranulated cytoplasm (↗). Dysmegakaryocytopoiesis: megakaryocyte with hyposegmented nucleus und hypogranulated cytoplasm (↗ ↗). **d** Micromegakaryocyte (↗). Myelocyte with asynchronism of nucleo-cytoplasmic maturation (↗ ↗). Giemsa ×750

Fig. 3. Lymphoid cluster: some lymphocytes have a "monocytoid appearance" with a lobated nucleus and rather abundant cytoplasm (↗). A large cell with a cytomegalic inclusion is seen at the top right. Giemsa ×750

derin or "blue" ceroid pigments) and very exceptionally hematic cell debris (haemophagocytosis) were seen in the cytoplasm of macrophages. Case No. 14 showed clusters of histiocytes, but no infective agent could be detected. In case No. 15, one small epithelioid granuloma was observed, without any visible infective agent. In this case, a bone marrow culture was performed and was found negative, but Mycobacterium tuberculosis hominis was demonstrated in a lymph node biopsy. We did not find any area of marrow necrosis in our series.

Two main types of stromal abnormalities were observed: fibrosis and gelatinous transformation. Fibrosis of the reticulin type was present in 15 of the 18 patients (Fig. 4). In 11 of them, it was slight (2+ according to Bauermeister 1971) and in other 4 patients it was more marked (3+ according to Bauermeister), with a diffuse fiber network and scattered thick fibers. In 3 patients, the reticulin pattern was found normal, with no demonstrable fibers or occasional fine individual fibers. Dry-taps were noted in 3 of 4 patients with 3+ fibrosis (No. 7, 11 and 14). Seven patients (No. 7, 8, 10, 11, 16, 17 and 18) displayed the earlier stage of the so-called gelatinous transformation (gelatinous degeneration or serous atrophy), as de-



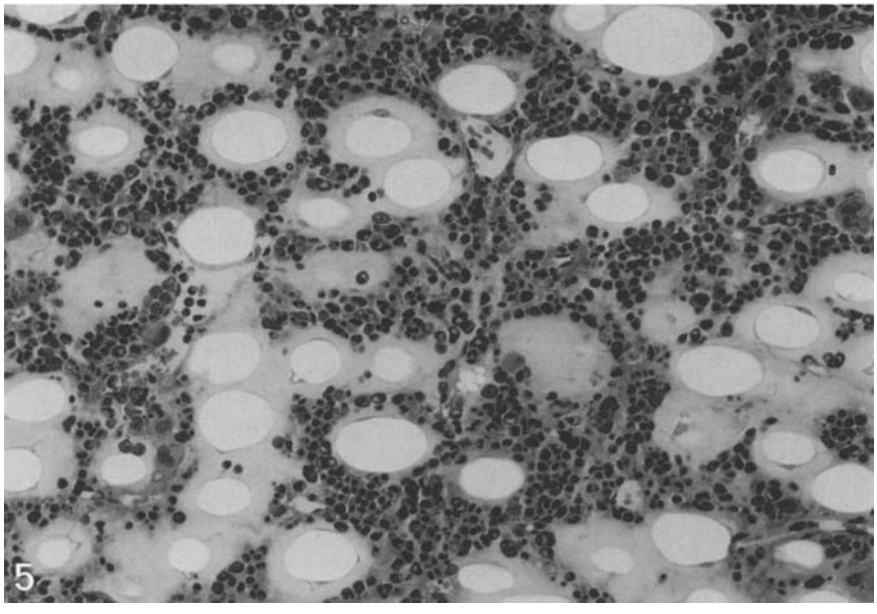


Fig. 4. Fibrosis of the reticulin type, with a diffuse fiber network and scattered thick fibers. The aspiration was dry. Gomori ×190

Fig. 5. Early stage of the gelatinous transformation (serous atrophy). A pale, amorphous substance is visible around fat cells. Giemsa ×150

fined by Seaman et al. (1978). A moderate amount of a pale, amorphous and slightly PAS positive substance was observed around isolated or small clusters of fat cells (Fig. 5). The lesion was diffuse in 4 and focal in 3 cases. Though the marrow appeared slightly atrophic in some areas of gelatinous transformation, the total amount of haematopoietic tissue was considered normal or slightly increased in the 7 cases. Vascular dilatation was additional stromal feature in 12 of the 18 cases. Iron stores were considered increased in 10, present in 5 and absent in 3 cases. No ring sideroblasts were observed. Special stains (Ziehl-Neelsen and PAS) did not reveal any infective agent in the 18 bone marrow biopsies. No excess of blasts, no malignant lymphoma and no Kaposi's sarcoma was seen.

Five patients (No. 7, 8, 10, 15 and 16) had a post mortem examination and we had opportunity to re-examine the bone marrow at that time. Hypercellularity was present in all 5, with a dissociated pattern of fat tissue in 4 of them (No. 7, 8, 10 and 16) and fibrosis was still present in 3 (No. 7, 15 and 16). Gelatinous transformation had regressed in 3 of the 4 patients, who had presented it on biopsy (No. 7, 8 and 16) but in one patient (No. 10) it was strongly accentuated, with large

lakes of an amorphous extra-cellular substance (Alcian Blue positive and slightly PAS positive). No tumour, no excess of blasts, no granulomata and no infective agents were found in the bone marrow of the 5 autopsied patients. Autolysis precluded the analysis of the dysmyelopoietic features. Cachexia was found to be present in patients No. 7, 8 and 10.

Discussion

Twelve (66%) of our 18 patients (10 with and 2 without cytopaenia and all belonging to CDC group IV) exhibited a constellation of marrow findings including normo- to hypercellularity, myelodysplasia, lympho- and/or plasmacytosis and fibrosis of the reticulin type. Gelatinous transformation was an additional feature encountered in 7 (38%) of the 18 patients.

Our results concerning the marrow cellularity and the number of megakaryocytes, which was normal or increased in most patients, are consistent with the data of the literature (Abrams et al. 1984; Castella et al. 1985; Schneider and Picker 1985; Shenoy and Lin 1987; Spivak et al. 1984). Hypocellularity was not found in our series and is mentioned in a minority of cases in previous reports (Castella et al. 1985; Osborne et al. 1984; Shenoy and Lin 1987; Spivak et al. 1984). The pattern of marrow hypercellularity, with fat cells dissociated by haematic cells, as described by Geller et al. (1985) in 53% of their biopsies, was encountered in only 6 (33%) of our 18 biopsies. The specificity of this pattern appears questionable, since Geller et al. (1985) have seen it in other conditions. Like Abrams et al. (1984) and Castella et al. (1985), we found a normal myelo-erythroid ratio and like Geller et al. (1985) and Spivak et al. (1984), a shift to the left of the granulocytic line and an increased number of eosinophils in many of our cases.

Until now, myelodysplasia in HIV infection has been described only on marrow smears (Schneider and Picker 1985). It has not been mentioned in previous histological studies, using decalcified and paraffin embedded biopsies, but it was a constant finding in our series of plastic embedded specimens. We wish to emphasize that the term "myelodysplasia" is used in a descriptive fashion and does not necessarily imply a premalignant condition. Dysmegakaryocytopoiesis and dyserythropoisis were the most common features, seen in 88% and 83% of the 18 patients respectively. Schneider and Picker (1985) in contrast found abnormalities of granulopoiesis more prevalent on marrow smears. This apparent discrepancy is not unexpected, since according to our experience (Delacrétaz et al. 1987), dysmegakaryocytopoiesis and dyserythropoiesis are easily detected on plastic sections, whereas dysgranulopoiesis may be underestimated.

Increased number of reactive cells is a common finding in bone marrow biopsies from HIV infected patients (Abrams et al. 1984; Castella et al. 1985; Geller et al. 1985; Osborne et al. 1984; Schneider and Picker 1985; Shenoy and Lin 1986; Spivak et al. 1984). It should be stressed that lymphoid clusters may be ill-defined and distributed at random in the marrow cavity, sometimes along the bone trabeculae and that the lymphoid population may present some pleomorphism (Osborne et al. 1984; Shenoy and Lin 1986). Granulomas and/or clusters of histiocytes, with or without microorganisms, have been found in 3 studies, beside ours (Castella et al. 1985; Osborne et al. 1984; Shenoy and Lin 1986). Histiocytosis with a haemophagocytosis has been described occasionally (Abrams et al. 1984; Spivak et al. 1984). Fibrosis of the reticulin type was a frequent feature in our study (15 of the 18 patients) as in most series of the literature (Abrams et al. 1984; Castella et al. 1985; Geller et al. 1985; Shenoy and Lin 1986; Spivak et al. 1984). The fibrosis appeared slight in most biopsies, but a dry-tap was noted in 3 of the 18 patients. Spivak et al. (1984) have reported a dry-tap in 3 of their 12 cases.

Gelatinous transformation (or gelatinous degeneration or serous atrophy) (Frisch et al. 1985; Peel and Krause 1981; Seaman et al. 1978) was a striking feature in 7 (38%) of our cases. These 7 patients were of the CDC group IV, with severe weight loss (5 patients) and/or infections (6 patients) and/or malignancy (3 patients). Gelatinous transformation corresponds to extracellular deposits of mucopolysaccharides and has been described in various diseases, including chronic inflammatory diseases, malignant diseases and anorexia nervosa. Serous atrophy has been mentioned in HIV infection (Osborne et al. 1984; Shenoy and Lin 1986; Spivak et al. 1984). Its pathology is not clearly understood. Cachexia and starvation play a role, but are probably not the only factors (Peel and Krause 1981; Seaman et al. 1978). As pointed out by Seaman et al. (1978), the marrow appears atrophic in the areas of gelatinous transformation, but the total amount of hematopoietic tissue may be still normal. The lesion is considered reversible (Peel and Krause 1981; Tavassoli et al. 1976); serous atrophy had subsided at autopsy in 3 of the 4 patients examined, despite the fact that 2 of these 3 patients had cachexia. In the fourth patient,

marked gelatinous transformation was present at autopsy together with cachexia.

The constellation of marrow features described here, although suggestive, is non specific and the differential diagnosis must take into account myelodysplastic and myeloproliferative syndromes among others. The final diagnosis of HIV infection cannot be established firmly without knowledge of the clinical and biological data. According to Osborne et al. (1984), differential diagnosis with lymphoma may be difficult in cases with atypical localisation (paratrabecular) of the lymphoid aggregates. Immunochemistry, which was not performed in this study, will probably be helpful in doubtful cases. It should be remembered that Di Carlo et al. (1987) have recently shown that bone marrow can be the initial anatomic site of malignant lymphoma in HIV infected patients.

The pathogenesis of the haematological abnormalities in HIV associated diseases is still unclear and probably multifactorial. Granulomatous marrow infiltration may be incriminated in one of our cases, in which the cytopaenia subsided after antituberculous therapy. In all the other cases, peripheral destruction and/or ineffective haematopoiesis must be postulated. An immune mechanism, in the peripheral blood, as proposed by Walsh et al. (1984), is suspected in 7 of our 10 thrombocytopaenic patients and hypersplenism in 4 of our 15 cytopaenic patients. Two patients had been exposed to Co-Trimoxazole, to which HIV infected patients are probably more sensitive (Jaffe et al. 1983) and this drug could have played a role in the causation of the cytopaenia.

Myelodysplasia and stroma disorders are strong indicators that bone marrow is a target site in HIV infection and/or HIV associated diseases. Like Schneider and Picker (1985), we found myelodysplasia to be the most intriguing feature, suggesting that marrow stem cells may be involved. Until now, one case of a myelodysplastic syndrome (Napoli et al. 1987) and one case of myelofibrosis (Solal-Céligny et al. 1986) have been reported in HIV infected and symptomatic patients. It is impossible to determine whether such associations are merely coincidental or reflect a relationship between HIV and marrow stem cell disease. HIV has recently been identified in macrophages of brain tissue from AIDS patients with encephalopathy (Koenig et al. 1986) and this observation suggests the possibility of an infection of marrow precursor cells by HIV. Furthermore, Donahue et al. (1987) have shown that antibodies to the gp120 glycoprotein of HIV suppress the growth of bone marrow cells derived from AIDS and ARC patients, presumably because of HIV infection of these cells.

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