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Intra-serous Haematopoiesis

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Abstract. *The samples from pleural and pericardial effusion, in which immature haematopoietic cells had been identified cytologically, were re-examined. The results were then analysed along with the clinico-biological context and compared to published data. The aim was to determine the frequency, the type and the context of haematopoietic cell identification in pleural and pericardial fluid effusion. In 10 years, 28 cases were studied. Four sub-groups were described: 1) patients with a severe sepsis, 2) patients with an acute local or regional infection, 3) persistent or recurrent effusion without specific context, 4) patients who underwent a transplantation treated with cyclosporin A. Even when the clinico-pathological context did not suggest a classical extra-medullary haematopoiesis, it was not exceptional to identify immature haematopoietic cells. This hypothesis is supported by published data, which suggests that a local inflammatory state could help mesothelial cells to constitute a favourable environment for division and maturation of circulating haematopoietic progenitor cells.*

Extra medullary haematopoiesis (EMH) is defined as the production of non-tumoral blood cells outside of bone marrow. This phenomenon has been documented for a long time and mainly occurs in reticulo-endothelial tissues: spleen, liver and lymph nodes, which are haematopoietic organs during foetal life (from the 3rd to the 6th month *in-utero*) (1). Less frequently, EMH may constitute a para-vertebral pseudo-tumoral mass (2,3). Much less frequently, EMH may constitute intra-tissular masses: pleural (4-7), pericardial (8), mammary (9), cutaneous (10), bladder (11). Usually this phenomenon is explained by its compensating action, even though not very efficient, in terms of haematopoiesis. This is the case, on the one hand, when the haematopoietic medullary production is deficient [during myeloproliferative syndromes, especially Agnogenic Myeloid Metaplasia (AMM), or in tumoral medullary or chronic inflammatory infiltration (2)] or, on the other hand, when the peripheral destruction is increased (in thalassemia or in hereditary spherocytosis (3)).

In daily practice, it is not exceptional to identify haematopoietic cells from effusion fluids in patients *a priori* free from haematological disease, without any EMH mass revealed by imagery. The presence of these cells could be considered as a kind of EMH.

We selected, over a 10-year period, a series of 28 patients in whom immature haematopoietic cells had been identified from pericardial or pleural effusion, without any pseudo-tumoral mass revealed by imagery. We tried to analyse non-medullary factors which could be responsible for this phenomenon.

Materials and Methods

Over 10 years, in the Grenoble University Hospital, France, 5,938 pleural and pericardial samples from effusion were examined. Among these, 28 met the following criteria: 1) identification of non-malignant haematopoietic cells from erythrocytic, and/or granulocytic, and/or megacaryocytic lineages; 2) lack of any pseudo-tumoral mass revealed by imagery, on the thoracic level, suggestive of EMH; 3) blood contamination after puncture negative according to haemogram data.

The examined slides were made by spreading the centrifugation sediment or by cytocentrifugation. They were then stained by May Grunwald Giemsa or, more seldom, by Papanicolaou. In one case, an immunocytochemical study was made to identify glycophorine A.

A semi-quantitative analysis was made with: +++: haematopoietic cells, whatever the lineage, were present in all fields, magnification X100; ++: haematopoietic cells were present in some fields at X100; +: haematopoietic cells were rarely present in any fields at X100.

Results

Over 10 years, after examining 5,938 pleural and pericardial samples from effusion, 28 were found to include haematopoietic cells, in the absence of any pseudo-tumoral mass revealed by imagery or histology (Table I). The patients' ages ranged from 27 to 84 years, average 59 years.

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Table I. *Patient characteristics. pl: pleural effusion; per: pericardial effusion AML: acute myeloid leukaemia; CR: complete remission; T-NHML: T-cell non Hodgkin malignant lymphoma; AMM: agnogenic myeloid metaplasia; cyclo A: cyclosporin A; AF: auricular fibrillation; Megacaryocyte: cell of the megacaryocytic lineage; Normoblast: normoblast= red cell precursor at any stage; RBC: red blood cell; ND: not determined; WBC: white blood cell; ↓ decrease; ↑ increase.*

Cases/ site	Age	History	Context	Blood Marrow analysis	Bone analysis	Cytology
I / pleu	27	T-NHML	post-chemotherapy septic shock	Agranulocytosis ↓platelets	ND	Promyelo/myelo +
II / pleu	42	Crohn's disease	Sepsis due to peritonitis	↑WBC myelocytes1%	ND	Myeloblast to myelocyte ++ Normoblast +
III / per	36	Dilated myocardial disease	Sepsis	↓RBC; ↑WBC	ND	Myeloblast to metamyelocyte +++
IV / pleu	78	Chemotherapy for 1 month	Sepsis on peritonitis	↑WBC myelocytes (rare)	ND	Myelocyte +++ Normoblast +
V / pleu	80	Myelodysplastic syndrome	Febrile pleuresia	↓RBC, platelets	ND	Myelocyte+
VI/pleu	32	Hodgkin lymphoma chemotherapy	Pleuropercarditis + persistent effusion	↓platelets myelocytes	ND	Myelocyte + Normoblasts +
VII/pleu	73	Myelodysplastic syndrome	Pneumonia	↓WBC, ↓platelet Normal	ND	Myeloblast to myelocyte ++
VIII / pleu	49	-	Super infected pulmonary emboli	↑WBC	ND	Myelocyte +
IX / pleu	40	Bronchopulmonary carcinoma and chemotherapy treatment	Pneumonia	Normal	ND	Myeloblast to myelocyte +
X / pleu	83	-	Pneumonia	Normal	ND	Promyelocyte to myelocyte +++ Normoblast +
XI / pleu	80	BPCO	Purulent pleuresia	Normal	ND	Promyelocyte and myelocytes ++ Normoblasts +
XII / pleu	76	AMM	Recurrent pleural effusion	↓RBC, platelets, WBC	Weak	Myelocytes ++ Normoblasts +++
XIII / pleu	80	Myelodysplastic syndrome	Chronic pleural effusion	Normal	Dyserythr-opoiesis	Promyelocytes to Metamyelocytes ++; Normoblasts + Megacaryocytes +
XIV / pleu	77	Myeloproliferative disease	Chronic pleural effusion Pachypleuritis	↑RBC	ND	Promyelocytes to metamyelocytes +++ Normoblasts +
XV / per	84	Peritoneal dialysis secondary to IRC	Chronic pericardial effusion for 4 months	Normal	ND	Promyelocytes and myelocytes ++ Normoblasts ++
XVI/ pleu	74	cardiac, renal insufficiency; peritoneal dialysis	New anasarcous state	↓platelets	ND	Myeloblasts and promyelocytes +++ Normoblasts +++

Table I. *continued*

Cases/ site	Age	History	Context	Blood Marrow analysis	Bone analysis	Cytology
XVII / per	64	Constrictive chronic pericarditis	Post-pericardectomy	Normal	ND	Promyelocytes and myelocytes ++ Normoblasts +
XVIII / per	33	Toxicomania	Recurrent pleuresia and pneumonia	↓RBC	ND	Myelocytes + Normoblasts +
XIX / pleu	33	HIV +, visceral leishmaniasis	Recurrent pleural effusion	↓RBC	Normal	Promyelocytes and myelocytes + Normoblasts +
XX /pleu	47	Alcoholic cirrhosis	Recurrent pleural-ascites	Normal	Normal	Promyelocytes myelocytes +
XXI / pleu	71	-	Rib fracture<trauma	Normal	ND	Promyelocytes +++
XXII / per	84	-	AF	Normal	ND	Myelocytes + Normoblasts +
XXIII / pleu	75	Bronchopulmonary carcinoma	Post-operative lobectomy	Normal	ND	Myeloblasts to metamyelocytes +++ Normoblasts +++ ; Megacaryocytes
XXIV / pleu	32	AML autograft ; CR for 5 years	Bipulmonary graft for 1month cyclo A higher dose	↓RBC, platelets, WBC	Normal	Myeloblasts+++
XXV /per	31	AML allograft in CR	Pericardial effusion	↓RBC, ↓platelets Myelocytes (rare < 1%	ND	Promyelocytes and myelocytes +
XXVI / pleu	63	Autoimmune cirrhosis	Hepatic transplantation; shock state of unknown origin	↓platelets, ↑WBC	ND	Promyelocytes and myelocytes + Normoblasts +
XXVII/ per	58	Bipulmonary graft for 2 months	Chronic pericardial effusion for 2 months	Normal	ND	Myelocytes ++ Normoblasts ++ ; Megacaryocytes
XXVIII / pleu	55	Sclerosing cholangitis	Pneumonia at D15 post- hepatic graft	↓RBC	ND	Promyelocytes and myelocytes +

An analysis of the occurrence context of these effusions allowed the determination of 4 sub-groups : 1) severe sepsis: cases I to IV; 2) acute local or regional infection: cases V to XI; 3) no specific context with persistent or recurrent effusion: cases XII to XXIII ; 4) graft/transplantation: cases XXIV to XXVIII.

Severe sepsis, with or without a state of shock, was found in 5 patients; except for case I in whom sepsis was due to post-chemotherapy agranulocytosis, patients presented with hyperleukocytosis. Rare circulatory haematopoietic cells were isolated in cases II and IV (myelocytes only); cytological examination of effusion, in these cases, revealed elements of granulopoietic lineage, at early stages of maturation (myeloblasts, promyelocytes), associated with elements of erythrocytic lineage (Figure 1A). In the other cases, the immature granulopoietic elements were also present, at various stages. In a few cases, granulocytic elements surrounding a mesothelial cell were seen (Figure 1B).

In acute local or regional infection cases (pleuresia, pneumonia, pleuro-pericarditis) the granulopoietic lineage

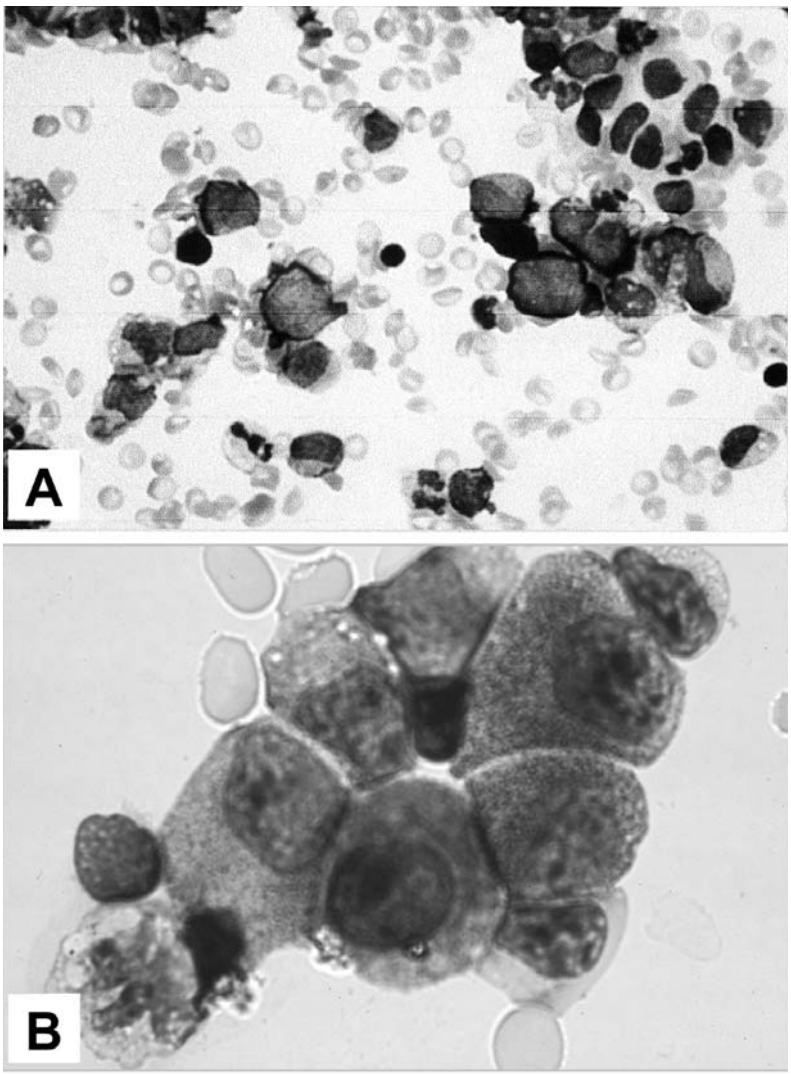

Figure 1. *A. Pleural effusion of case XXIII. X40 magnification. Immature granulocytic cells are associated with immature erythroblastic cell lineage. B. Pleural effusion of case XXIII. X40 magnification. Immature granulocytic cells surrounding a mesothelial cell.*

were also the most frequently identified, though usually in isolated cases and small number. The delay between the onset of clinical signs and the puncture ranged from 2 to 15 days. Cases X and XI represent these 2 extremes and, for both, the granulopoietic precursors were present in large numbers and associated with the erythrocytic lineage. Thus, no correlation can be made between the duration of effusion and its haematopoietic cell content.

Persistent or recurrent effusion induces a local inflammatory process and long-term irritation of the pleural mesothelium. The delay between the onset of clinical signs and the puncture proving the presence of haematopoietic cells ranged from 3 weeks to 24 months. But, in this context, it is difficult to find the exact date of effusion onset, because it is often revealed late (dyspnea, signs of cardiac insufficiency). We can suppose that the reported delays were under evaluated. For case XX, the pleural effusion followed persistent ascites; case XVI was comparable since, besides his weakened state, the patient had undergone regular peritoneal dialyses for several months. Nevertheless, for these 2 patients, the delay between the diagnosis of effusion and puncture was short. During these chronic or recurrent effusions, qualitative and quantitative data concerning the isolated haematopoietic cells were heterogeneous. These cells were scarce and there was often an association with granulopoietic lineage / erythrocytic lineage, or megacaryocytic lineage for case XIII. Furthermore, the elements were present at various stages of maturation.

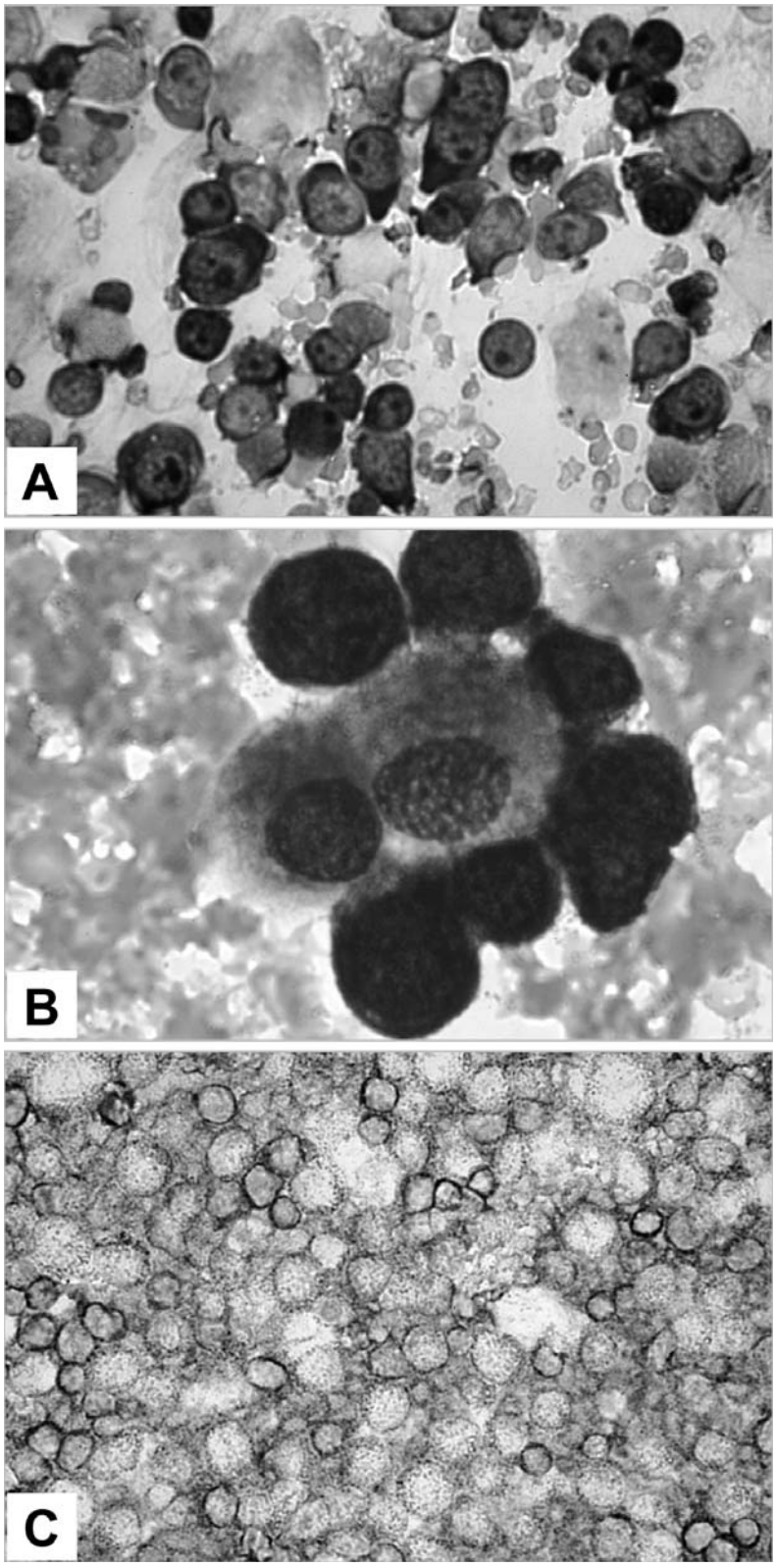

Figure 2. A. Pleural effusion of case XII. X40 magnification. Essentially pronormoblasts are seen. B. Pleural effusion of case XII. X100 magnification. Pronormoblasts surrounding a mesothelial cell. C. Pleural effusion of case XII. X20 magnification. Immunostaining for glycophorin A detection. All the cells are positive.

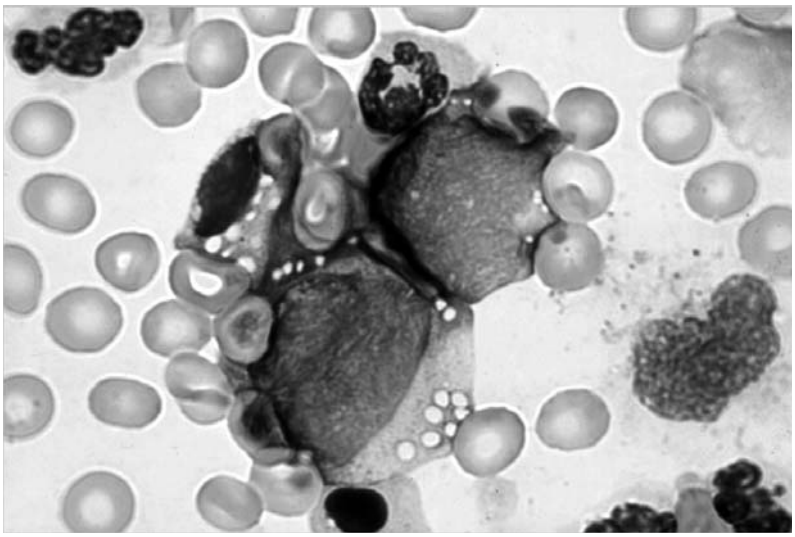

Figure 3. *Pleural effusion of case XXIV. X20 magnification. At the first pleural puncture only myeloblasts were seen.*

Given the chronicity of their clinical symptoms, patients XII to XV and XIX underwent a pleural or pericardial biopsy. The histological examination did not reveal any myeloid metaplasia. Case XII was interesting, showing especially pronormoblasts (Figure 2A) identified by immunocytochemistry (antibodies againts glycophorin A were used Figure 2B). As in Figure 1 numerous immature cells surrounded a mesothelial cell (Figure 2C). In case XXIII, the broncho-pulmonary carcinoma did not invade the pleura and was associated with effusion sampled per-operatively. The length of effusion was not documented, but a persistent local inflammation was probable. So this case was comparable to the sub-group previously analysed. In case XXI, a rib fracture occurred 5 days before the onset of effusion. The possibility of pleural injury due to the trauma, with contamination of the effusion by haematopoietic tissue, is improbable because there was no pneumothorax. Furthermore, cytological assessment of the puncture fluid revealed only promyelocytes and no element from other lineages.

The grafted and/or transplanted patients (5 cases) were all given cyclosporin A (Figure 3). Cases XXVII and XXVIII presented with persistent effusion and an acute local or regional infectious focus, respectively. Effusion was acute and non infectious in the other cases. Cytological assessment of the sampled fluids revealed that elements of the granulopoietic lineage were the most frequently isolated, in variable proportions, and associated with elements of erythrocytic and megacaryocytic lineages (multi-lineage haematopoiesis) for caseXXVII. A pericardial biopsy was performed for this patient but did not reveal any myeloid metaplasia. In case XXIV, a false-diagnosis of relapse leukaemia was made on the basis of numerous myeloblastic cells identification (Figure 3). A second pleural puncture a few days later showed granulocytic cells at different maturation stage, which confirmed an EMH.

In every case, whatever the clinical symptoms or the duration of effusion evolution, cells of the granulopoietic lineage were present, sometimes associated with elements of erythrocytic and, more rarely, megacaryocytic lineage. Nevertheless, it was not possible to correlate the context of effusion onset to maturation stages or to the quantitative aspect.

Nine patients out of 28 (I, V, VI, VII,XII, XIII, XIV, XXIV, XXV) presented with a history of haematological disease, evolving or in clinical remission, with more or less severe bone marrow insufficiency. Case IX also presented a bone marrow insufficiency due to chemotherapy.

Out of the 28 patients, circulatory haematopoietic precursors were isolated on haemogram in only 5 patients (II, IV, VI, VII, XXV), without any quantitative or qualitative concordance with those found in the puncture fluids.

Discussion

Haematopoietic cells are rarely isolated in intra-serous effusion (around 0.5% in our study). In the literature, their presence is often related to an Agnogenic Myeloid Metaplasia (AMM), and Silverman suggested that the term "extra medullary haematopoietic effusion" be used in those circumstances (12). The other etiologies involving EMH are those where there is a discrepancy between bone marrow

production and peripheral needs. EMH would then play a compensating role (1,5): myeloproliferative disorders (2,4,7), medullary tumoral invasion (13), chronic medullary inflammation, haemolytic anaemia (2), or even cyanogenic cardiac disease in children (14).

In our study, EMH was only identified through cytological examination. In almost every case, a possible contamination during the procedure could be ruled out on the basis of a haemogram which was done in conjunction with effusion cytology analysis.

In every case, thorax imagery such as scan or echocardiography was done and did not reveal any pseudo-tumoral mass. When performed, mesothelial layer biopsies did not reveal any tissular localization of EMH. Bone marrow examination was rarely performed, but in cases XXIV, XIX and XX it did not document any of the above-mentioned diseases.

There is no single explanation for the histogenesis of EMH. In 1983, Walker *et al.* suggested the existence of extra medullary stem cells able to differentiate into haematopoietic cells in a compensating process case (7). This idea was used by Wolf and Nieman for their " filtration theory" in 1985: spleen and liver trap circulatory haematopoietic cells and produce an environment favourable for their differentiation (15). In 1998, Ida Hsu *et al.* reporting on a para vertebral and pleural EMH case associated to a broncho-pulmonary carcinoma, suggested the possibility that a paracrine carcinomatous factor would promote a regional hyperplasia of circulatory haematopoietic progenitors. Finally, in 1999, Ben Rejeb *et al.* wrote about a re-expression of the foetal haematopoiesis process due to a metaplasia of mesenchymal cells (2).

The compensatory haematopoiesis hypothesis could not be applied to all the cases in our study, and especially not for patients presenting with a normal bone marrow state assessment. Furthermore, the compensation, when present, was never total and would not explain the normal haemogram. The notions of favourable environment and of paracrine factor seemed more adapted to our cases. In the literature, some arguments exist in favour of our hypothesis. Demetri *et al.*, in 1998, showed, *in vitro*, that mesothelial cells spontaneously synthesized Macrophage-Colony Stimulating Factor (M-CSF), and that their exposition to inflammation mediators (Tumour Necrosis Factor, liposaccharides) increases the level of expression of various haematopoietic factors (16). In 1992, Lanfrancone demonstrated the local production of other cytokines: Granulocyte-CSF (G-CSF), Granulocyte/Macrophage-CSF (GM-CSF), Interleukin-1 (IL-1) and IL-6. He also showed that G-CSF and GM-CSF expression increased with the length of culture, and that a strong stimulus due to IL-1, as met in persistent inflammatory phenomena, increased their production as well as that of IL-6, making the haematopoietic precursor more susceptible to growth factors (17).

Since mesothelial cells spontaneously synthesize various actives cytokines on granulopoietic progenitors, they are able to create a favourable environment for their maturation and differentiation. The presence of haematopoietic precursors in blood is a rare event. If we consider Wolf and Nieman's filtration theory, we can suppose that these precursors can fix themselves when adequate cytokine concentrations are present (in our cases, on pericardial and pleural layers). In cases of local or general inflammation, the presence of IL-1 could lead to increase and optimise this process, inducing more often a local granulopoiesis.

The analysis of the 28 selected cases allowed the determination of 4 different contexts where haematopoietic cells are present in effusion: 1) severe sepsis; 2) acute local or regional infection; 3) no specific context with persistent or recurrent effusion; 4) transplantation/graft under cyclosporin A treatment. The last sub-group received an immunosuppressive treatment; the other 3 presented with an acute or chronic local , or severe general inflammatory state.

Among our patients as well as in common practice, the main etiologies of pleural or pericardial effusion are inflammatory, more or less associated with an infectious state. Given the above data, local granulopoiesis should be more frequently identified. Nevertheless, in our study this process was rare: 0.5% of the samples over 10 years, all of which contained elements of the granulopoietic lineage. Even if the mesothelium is able to produce cytokines, this tissue is not the best suited and probably does not generate strong cellular interactions compared to the bone marrow environnement. This could explain the scarcity of the process in all effusions.

It is acknowledged that, in bone marrow, erythropoiesis takes place in "erythroblastic islets" made of a central macrophage surrounded by erythroblasts in differentiation and maturation. In 1994 and 1998, Hanspal demonstrated erythroblast/macrophage cellular interaction: it takes place using a cellular adhesion protein called Emp (Erythroblast macrophage protein)(18,19). This cellular interaction could trigger erythrocytic proliferation and maturation by allowing nucleus expulsion at the acidophilic erythroblast stage. Without this interaction the cells would go into apoptosis. In our study, we were able to observe, even if rarely, a comparable aspect to that of medullary erythroblastic islets where a mesothelial cell holds the central position. Furthermore, we know that phagocytosis is a feature of the normal mesothelial cell. It was proved that intralysosomal inclusions in these cells sometimes corresponded to fragments of erythrocytic membrane (20). Mesothelial cells are thus capable of phagocyting acidophilic erythroblast nuclei during enucleation.

It would be of interest to look for Emp membrane expression in stimulated mesothelial cells: this could

demonstrate an active role of serous layers in extra medullary erythropoiesis.

No published data allowed us to form any hypothesis concerning megacaryocytic lineage development in mesothelium.

Besides the local or general inflammatory context described in most of the cases in our study, 5 patients had in common a cyclosporin A treatment secondary to transplantation. Among these, 2 presented with either pneumonia (case XXVIII) or chronic effusion (case XXVII) and could be included in the sub-group previously analysed. For the other 3, no concomitant inflammatory process could be documented.

In the literature, it has been described that cyclosporin A could play a role in these cases, by allowing an increase of bone marrow haematopoiesis. In 1994, Hashimoto *et al.* showed that, in the normal murine model, T lymphocytes (especially CD8 +) act as negative regulators of haematopoiesis. The number of these lymphocytes decreases during cyclosporin A treatment (21). In the same way, in 1999 Perry *et al.* showed that, *in vitro*, low doses of cyclosporin A may stimulate the growth of haematopoietic cells in a favourable medium (22).

Thus, through its immunosuppressive effect, cyclosporin could stimulate central haematopoiesis and could allow an increased circulation of precursor cells in peripheral blood (23). These precursors would only need to find a favourable extra medullary environment (mesothelial in our study) to fix themselves and differentiate, also helped in this by cyclosporin.

Thus, at least theoretically, inflammation and cyclosporin A may contribute to extra medullary production and maturation of haematopoietic cells.

When the presence of haematopoietic cells is revealed by cytological examination, it is necessary to rule out differential diagnosis: (a) contamination by blood circulating during the puncture: it is of importance that a concomitant reference haemogram be available for the comparison; (b) contamination by bone marrow during the puncture: possible, especially in children and elderly people; (c) the isolated presence of megacaryocytic is not sufficient to diagnose an EMH: because of their size, these cells are frequently trapped in pulmonary capillaries, with the possibility of passing into a serous cavity through microruptures (24,25); (d) megacaryocytic should be distinguished from other multinucleated cells, malignant or not: benign multinucleated mesothelial cells, histiocytes and Reed-Sternberg cells (24, 26), even using anti-Factor VIII immunolabelling; (e) a large number of mature granulopoietic cells should suggest the presence of a local infectious process (27); (f) haematopoietic cells should be distinguished from poorly-differentiated tumoral cells (role of immunocytochemistry), or a granulocytic sarcoma (in which elements of erythrocytic and megacaryocytic lineages are absent) (8).

Morphology alone is usually enough to prove the diagnosis, but in doubtful cases immunocytochemistry should be used.

Conclusion

Using published data and the 28 cases included in our study, several hypotheses may be formed to explain the presence of haematopoietic cells in pericardial or pleural effusion. Besides patent bone marrow insufficiency with pseudo-tumoral EMH, we suggest that local or general inflammatory states, or acute infectious states, promote and generate haematopoiesis at the level of mesothelial layers, especially for granulopoietic lineage. This could be linked to the synthesis of haematopoietic growth factors by mesothelial cells. Furthermore, cyclosporin A, because of its immunosuppressive action, could promote an increase of haematopoiesis and of the number of circulating haematopoietic cells.

Could the absence of pseudo-tumoral EMH in these cases be due to a too short length of evolution at the time of examination? Or could the causal process be too limited in time, reversible, or of too weak intensity? Some patients in our study benefited from later punctures, which documented either the absence of haematopoietic cells or the progression of their maturation.

It is essential to remain vigilant when blood cell precursors are identified in effusion and to rule out differential diagnostics. It is then necessary to look for pseudo-tumoral EMH (using chest X-ray examination, analysis of the clinico-biological context), the isolation of which would require the performance of a bone marrow trephine biopsy.

References

1 Lemos LB, Baliga M, Benghuzzi HA and Cason Z: Nodular hematopoiesis of the liver diagnosed by fine needle aspiration cytology. Diagn Cytopathol *16*: 51-54, 1997.

2 Ben Rejeb A, Haouala H, Ben Hammidi F, Ben Othman M, Khelil A, Gueddiche M, Ben Cheikh M and Rokbani L: L'hématopoïèse extramédullaire pseudo-tumorale. Ann Pathol *12(3)*: 183-187, 1992.

3 Verani R, Olson J and Moake JL: Intrathoracic extramedullary hematopoiesis. Report of a case in a patient with sickle-cell disease-β-thalassemia. Am J Clin Pathol *73*: 133-137, 1980.

4 Bartlett RP, Greipp PR, Tefferi A, Cupps RE, Mullan BP and Trastek VF: Extramedullary hematopoiesis manifesting as a symptomatic pleural effusion. Mayo Clin Proc *70*: 1161-1164, 1995.

5 Ida Hsu F, Filippa DA, Castro-Malaspina H and Downey RJ: Extramedullary hematopoiesis mimicking metastatic lung carcinoma. Ann Thor Surg *66*: 1411-1413, 1998.

6 Kupferschmid JP, Shahian DM and Villanueva AG: Massive hemothorax associated with intrathoracic extramedullary hematopoiesis involving the pleura. Chest *103(3)*: 974-975, 1993.

7 Walker AN, Feldman PS and Walker GK: Fine needle aspiration of thoracic extramedullary hematopoiesis. Acta Cytol *27(2)*: 170-172, 1983.
8 Bradford CR, Smith SR and Wallis JP: Pericardial extramedullary haemopoiesis in chronic myelomonocytic leukemia. J Clin Pathol *46*: 674-675, 1993.
9 Martinelli G, Santini D, Bazzocchi F, Pileri S and Casanova S: Myeloid metaplasia of the breast. Virchows Arch [Pathol Anat] *401*: 203-207, 1983.
10 Kuo T, Uhlemann J and Reinhard EH: Cutaneous extramedullary hematopoiesis. Arch Dematol *112*: 1302-1303, 1976.
11 Mak YK, Chan CH, So CC, Chan MK and Chu YC: Idiopathic myelofibrosis with extramedullary haemopoiesis involving the urinary bladder in a chinese lady. Clin Lab Haem *24*: 55-59, 2002.
12 Silverman JF: Extramedullary hematopoietic ascitic fluid cytology in myelofibrosis. Am J Clin Pathol *84*: 125-128, 1985.
13 Garcia-Riego A, Cuinas C, Vilanova JJ and Ibarrola R: Extramedullary hematopoietic effusions. Acta Cytol *42(5)*: 1116-1120, 1998.
14 Luban NLC, Kapur S and DePalma L: Pericardial extramedullary hematopoiesis in a neonate with congenital heart disease. Acta Cytol *37(5)*: 729-731, 1993.
15 Wolf BC and Neiman RS: Myelofibrosis with myeloid metaplasia: pathophysiologic implications of the correlation between bone marrow changes and progression of splenomegaly. Blood *65(4)*: 803-809, 1985.
16 Demetri GD, Zenzie BW, Rheinwald JG and Griffin JD: Expression of colony-stimulating factor genes by human mesothelial cells and human malignant mesothelioma cells *in vitro*. Blood *74(3)*: 940-946, 1989.
17 Lanfrancone L, Boraschi D, Ghiara P, Grignani F, Peri G, Mantovani A and Pelicci PG: Human peritoneal mesothelial cells produce many cytokines (Granulocyte-Colony-Stimulating Factor [CSF], Granulocyte-Monocyte-CSF, Macrophage-CSF, Interleukine-1 [IL-1], and IL-6) and are activated and stimulated to growth by IL-1. Blood *80(11)*: 2835-2842, 1992.
18 Hanspal M and Hanspal J: The association of erythroblast with macrophages promotes erythroid proliferation and maturation: a 30-kD heparin-binding protein is involved in this contact. Blood *84(10)*: 3494-3504, 1994.
19 Hanspal M, Smockova Y and Uong Q : Molecular identification and functional characterization of a novel protein that mediates the attachment of erythroblasts to macrophages. Blood *92(8)*: 2940-2950, 1998.
20 Zaharopoulos P, Wen JW and Wong J: Membranous lamellar cytoplasmic inclusions in histiocytes and mesothelial cells of serous fluids. Their relationship to phagocytosis of red blood cells. Acta Cytol *42(3)*: 607-613, 1998.
21 Hashimoto F, Sugiura K and Ikehara S: Enhancing effects of cyclosporin-A on hematopoietic progenitors : possible role of CD8+ T cells as negative regulators. Exp Hematol *22(10)*: 947-953, 1994.
22 Perry SS, Kim M and Spangrude GJ: Direct effects of cyclosporin-A on proliferation of hematopoietic stem and progenitor cells. Cell Transplant *8(4)*: 339-344, 1999. (Abstract).
23 Jonasova A, Neuwirtova R, Cermak J, Vozobulova V, Mocikova K, Siskova M and Hochova I: Cyclosporin-A therapy in hypoplastic MDS patients and certain refractory anaemias without hypoplastic bone marrow. Br J Haematol *100*: 304-309, 1998.
24 Adams LC, Tham KT, Ross PH and Flatter WD: Significance of megacaryocytes in pleural fluid. Acta Cytol *39*: 606-608, 1995.
25 Bartziota EV and Naylor B: Megacaryocytes in a hemoragic pleural effusion caused by anticoagulant overdose. Acta Cytol *30(2)*: 163-165, 1986.
26 Kumar NB and Naylor B: Megacaroycytes in pleural and peritoneal fluids: prevalence, significance, morphology, and cytohistological correlation. J Clin Pathol *33*: 1153-1159, 1980.
27 Raab SS, Silverman JF, McLeod DL and Geisinger KR: Fine-needle aspiration cytology of extramedullary hematopoiesis (Myeloid Metaplasia). Diagn Cytopathol *9*: 522-526, 1993.

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