Virchows Archiv A Pathol Anat (1990) 416:423–428

Virchows Archiv A
Pathological Anatomy and Histopathology

Deposition of lipopigment – a new feature of human splenic sinus endothelium (SSE)

Ultrastructural and histochemical study

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Received May 11, 1989 / Received in revised form October 31, 1989 / Accepted November 1, 1989

Summary. Lipopigment (LP) deposition was studied in a series of 36 control and 79 pathological spleens. In the control group the LP deposition in SSE was rudimentary and did not display age-dependence. A varying degree of lysosomal and cytoplasmic siderosis was a frequent finding in haemolytic anemia without any significant LP induction. In the acquired secondary storage syndrome and in some inherited lysosomal enzymopathies, the amount of LP in splenic sinus endothelium (SSE) was significantly increased and in some instances its deposition reached very high values. As deposition was not accompanied by any detectable lysosomal lipid storage phenomenon in pulpar histiocytes, the pigmentogenesis is thought to be by a process resembling that for lipofuscin. In ceroid-lipofuscinosis group the SSE affection was of low degree, as seen in other viscera. The LP deposition seems thus to be a prominent, albeit variable feature of human SSE lysosomal pathology and may represent a monotonous response to various stimuli connected with increased demands on the SSE lysosomal system. Only in some lysosomal enzymopathies, typically in sphingomyelinase deficiency was SSE LP deposited progressively and concurrently with the stored lipid. LP deposition was accompanied by an increase in lysosomal enzyme activities but lacked the alkaline phosphatase induction in SSE described in lipid and mucopolysacchride storage diseases. This and several other features which are reviewed clearly distinguish SSE from the pulpar histiocytes with which they have been often identified.

Key words: Human splenic sinus endothelium – Lipopigment

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Introduction

There is general consensus that the cardinal function of the splenic sinus endothelium (SSE) is to participate in monitoring the age-dependent physical properties of the red blood cells (Bloom and Fawcett 1986). This function is supposed to be exercised by the SSE-basement membrane complex which transmits only the fully compressible transversing elements, while others remain in the Billroth cords where they are scavenged by the resident phagocytes. What is not entirely clear is to what extent the SSE participates in the red pulp phagocytic potential. For years there exist two extreme and mutually incompatible hypotheses. One of them, dating back to Klemperer (1938), sees the SSE as sessile macrophages retaining their full phagocytic capacity (Lasser 1983; Weiss 1957). According to the other, which has been gaining ever widening acceptance, this traditional view is seen as no longer tenable (Bloom and Fawcett 1986; Burke and Simon 1970; Molnar and Rappaport 1972; Moore et al. 1961) and SSE is seen as a subgroup of the sinus endothelial cells which are reported to display higher lysosomal activity than the ordinary capillary endothelium (Bloom and Fawcett 1986).

Data on the range of the SEE lysosomal reactivity in various human pathological states characterized by increased demand on this cell digestive apparatus is scanty. The aim of this report is to add some new knowledge to this aspect of SSE pathology and, specifically, to draw attention to the yet unknown tendency of these cells to generate and accumulate lipopigment (LP) residual bodies.

Material and methods

A series of 115 spleens (see Results) were examined using conventional histology (paraffin embedding) and histochemistry (cryostat

sections, standard frozen sections, paraffin sections). The lipopigment was detected with the aid of its autofluorescence, apolarity with Sudan Black B (in 70% ethanol), acid resistence and staining with aldehydefuchsine after acidified permanganate preoxidation (Lillie 1965). The latter technique was used as most suitable for LP semiquantitation. Masson's ammoniacal silver technique and Gomori's hot silver methenamine reduction were in each case paralleled by the silver nitrate technique (5% silver nitrate in distilled water, see Lillie 1965). Iron was detected with both Perls and Turnbull methods, and the ferricyanide variant was also used after conversion to sulfide by yellow ammonium sulphide. Dithionite was used for a prompt removal of the iron (Lillie et al. 1963). This technique was employed for exclusion of any inhibitory effect of iron salts on LP detection (Elleder 1981).

The activities of acid and alkaline phosphatases were demonstrated with azocoupling methods the details of which are described elsewhere (Elleder 1979b). For ultrastructural studies the tissue samples (four to six per case) were fixed in 10% phosphate buffered paraformaldhehyde and 1% osmium tetroxide (bioptic and fresh postmortem samples). Tissues stored in formaldehyde were postfixed with osmium tetroxide. All specimens were dehydrated with ethanol and embedded into Araldite-Epon mixture. The thin sections were double contrasted with uranyl acetate and lead citrate.

Phospholipids were analysed by two-dimmensional thin layer chromatography as already described (Elleder et al. 1980).

Results

In typical cases qualification of a LP residual body as lipopigment poses no basic problems, even if only electron microscopy is used as a diagnostic tool because of the existence of well defined fine structural patterns (Boellaardt and Schlotte 1986; Goebel 1988). However, the full range of ultrastructural appearances is much wider then that usually recognized and the difference may be a source of diagnostic difficulties. For this reason and since LP is best defined by lipid histochemistry (Elleder 1977, 1981) the diagnosis was based primarily on histochemistry. All the ultrastructural findings were correlated and interpreted accordingly.

Histochemically the SSE residual granules exhibited yellow, orange or sometimes yellow green autofluorescence and were variably sudanophilic (specified below). They also displayed strong acid-resistence, argentaffinity with Gomori's silver methenamine, distinct positivity with aldehydfuchsin after preoxidation and slight PAS positivity. They sometimes reduced Masson's ammoniacal silver solution but never the silver nitrate. The ultrastructure was relatively monotonous – the LP mass generally displayed an almost homogeneous (occassionally rudimentary granular or membranous) structure which was focally dense. The dense parts often occupied the bulk of the granule. Typical medium dense homogenous lipid granules were rare. Sometimes the medium dense variants predominated, resembling serous exocrine granules at lower magnification. The residual bodies' size ranged from 0.3–1.3 μm (Fig. 1b, c). They were limited by a typical unit membrane of 7.5 nm thickness. The smallest bodies had much looser content with fragments of membranes 7–8 nm thick.

A series of thirty six control spleens with normal histology (24 malignancy, 6 ischaemic heart disease, 1 sclerodermia, 2 pyelonephritis, 3 liver cirrhosis) covering 60–96 years age range showed normal SSE free of any lysosomal deposits with the exception of rare granules with staining and fine structure corresponding to LP. The SSE ultrastructure, due to its repetitiveness, was studied in a selected series of ten cases and was found to be identical to that already described (Bloom and Fawcett 1986; Molnar and Rappaport 1972), pointing also to the extreme paucity of small lipofuscin granules (Fig. 1a). The acid phosphatase activity was barely detectable, that of alkaline phosphatase was absent.

The hereditary spherocytosis group (10 cases) displayed a varied degree of SSE activation. The red pulp histiocytes never showed storage phenomena except for haemosiderin deposition. In four cases the SSE harbored a moderate amount of strongly light-refraction tiny haemosiderin granules contrasting with strong diffuse cytoplasmic staining for iron, suggesting massive extralysosomal siderosis. In the remaining six cases the SSE was free of iron deposition. After removal of iron with dithionite there was virtually no LP deposition detectable in the SSE (Table 1). A low degree of LP deposition was demonstrable in pulpar histiocytes. SSE ultrastructure was dominated by diffuse prominent cytoplasmic microvesiculation and conspicuous degree of pinocytosis present all over the SSE cell membrane, and by well developed Golgi apparatus. The lysosomal bodies were packed with dense fine granules well seen in uncontrasted sections. The same granules were also in appreciable quantities free in the cytoplasm. Signs of platelet and red blood cell internalization were relatively frequent, sometimes with signs of their destruction. Acid phosphatase activity was either undetectable or very slightly increased. Alkaline phosphatase activity was not demonstrated in SSE.

Acquired (secondary) storage with idiopathic thrombocytopaenic purpura (12 cases), encompassing both chronic (eleven) and acute (one) cases, featured storage histiocytes localized exclusively in the Billroth cords. The results of lipid histochemistry of the storage histiocytes were uniform: presence of phospholipids (sphingomyelin dominated) with a small admixture of glycolipids, cholesterol and ceroid. Quantitatively sphingomyelin was slightly increased ($4.92+2.36$ μmol/g, range 2.58–8.22; $n=4$) against controls ($1.49+0.5$; $n=6$) and never attained the values found in the Niemann-Pick complex (Elleder 1989; Vanier 1983). Concentrations of other phospholipids were not significantly changed. Ultrastructure of the histiocyte population was uniform and was represented by loosely packed membranous whorls. The ceroid granules consisted of relatively densely packed trilaminar membranes about 13–15 nm thick.

The SSE appeared entirely normal in routinely stained sections. In six cases, however, histochemistry showed discrete granules with properties corresponding to LP (see above) which due to a questionable sudanophilia were classified as lipofuscin. The staining for iron was negative. Semiquantitative evaluation of the SSE LP granules is given in Table 1 (see also Fig. 1). Acid phosphatase activity was increased proportionally to the

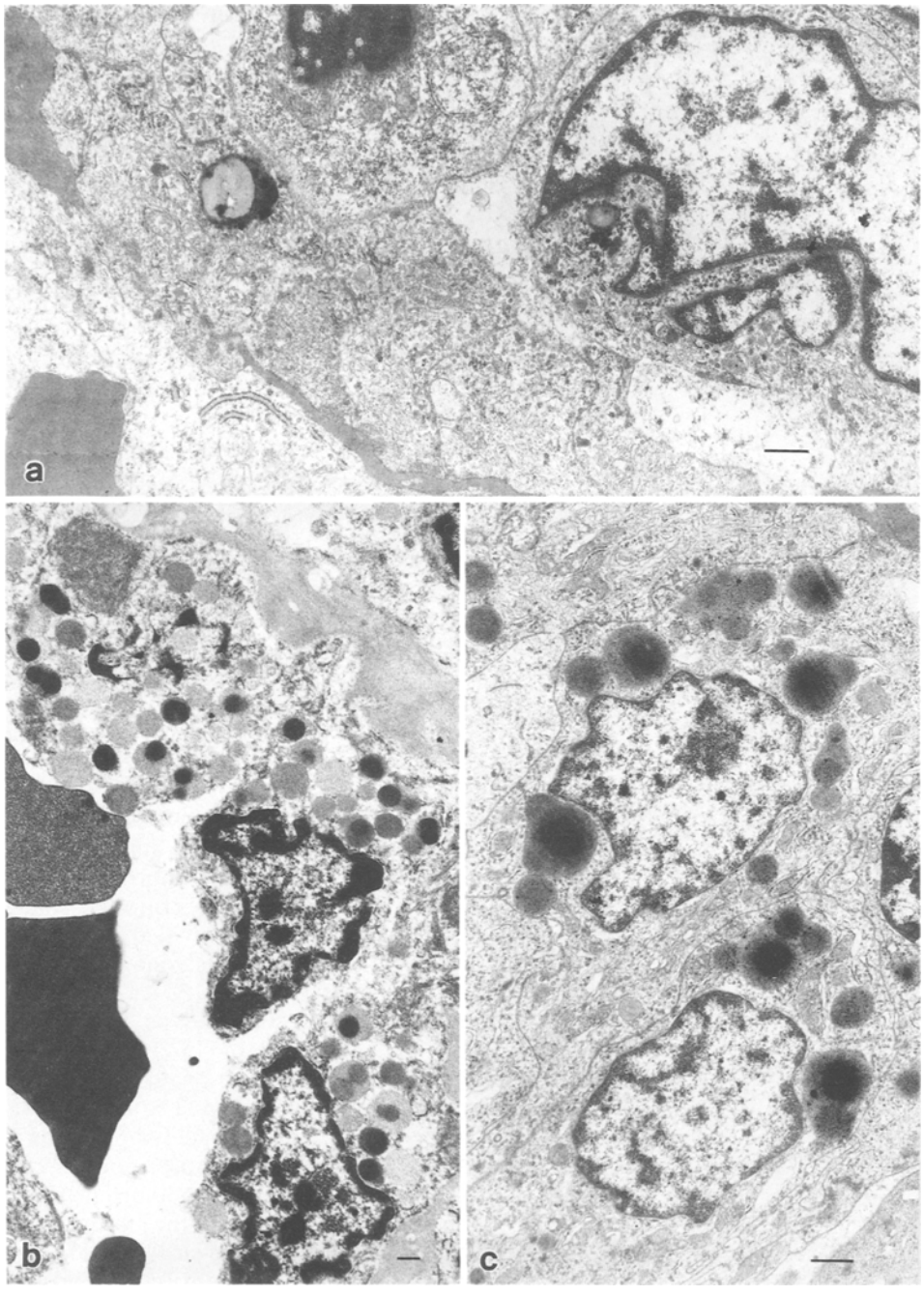

Fig. 1. Electronograms showing paucity of LP in control SSE (**a**) moderate amount of LP granules (1+, see Table 1) in a case of thrombocytopaenia (**c**) and the highest amount observed (2+) in a cholestatic hepatopathy with secondary storage (**b**) Bars = 1 μm

LP deposition degree. There was no alkaline phosphatase induction in SSE.

Ultrastructurally, none of the lysosomal lipid storage phenomena seen in pulpar histiocytes (see above) were seen in SSE. There were only variably sized lysosomal bodies of residual types with the fine structure above mentioned (see also Fig. 1c). Thrombocytes in the SSE in various stage of degradation were rare.

There was no correlation between the degree of SSE LP deposition and the duration of the haemorhagic diathesis or the shortening of the platelet survival time.

Spleen storage in the acquired (secondary) type without thrombocytopaenia (19 cases) was most probably due to hyperlipoproteinaemia, as in each case where biochemical data were available (12 cases) the only storage related abnormality was an increase in serum cholesterol (6–10 mMol/l) triglycerides (2–4 mMol/l) or both. Here, as in the preceding group, red pulp histiocyte storage was the main feature. The lipid storage pattern was very much like that in the preceding group. Due to formol fixation, only sphingomyelin was measured and was found to be only slightly increased (4.34+2.12 μmol/g wet weight; $n=6$). The storage was either a subsidiary finding at eleven autopsy cases (2 obstructive jaundice, 5 malignancy, 4 ischaemic heart disease) or was found in spleens surgically removed for traumatic rupture (2

Table 1. Semiquantitative evaluation of LP deposition in SSE. Neither of the lysosomal enzymopathies included expressed specific storage in SSE (numerals in columns represent number of cases)

	LP semiquantitative evaluation*			
	−	+	+	++
Controls	30	6		
Haemolytic anaemia	8	2		
Acquired spleen storage				
in ITT	3	3	2	4
without thrombocytopenia	5	5	4	5
Wolman's disease		1		
Gaucher's disease**	2			
Sulphatidosis			2	
Mucosulphatidosis***			3	
GM gangliosidosis****		2		
NPD type B (juven, var,)			1	
NPD type C				
Adult variant			1	
Juvenile variant			1	
Ceroid-lipofuscinosis		5	6	

ITT idiopathic thrombocytopenic purpura
NPD Niemann-Pick disease
* − LP absent, + 1–2 LP granules per cell, + numerous LP granules per cell leaving still some cytoplasm free, ++ cytoplasm filled up with LP granules without cell distension
** types 1 and 2
*** siblings
**** variants B and B_1

Table 2. Semiquantitative evaluation of enzyme substrate storage and LP deposition in lysosomal enzymopathies

	LP deposition*	Storage intensity*
Mucopolysaccharidosis		
type I ($n=3$)	−	++/+++
type III A ($n=1$)	−	++
GM gangliosidosis		
infantile ($n=1$)	−	++
Fabry's disease ($n=2$)	+/+	+/+++
Niemann-Pick disease type C late infant. var.		
case R.B.	−	+/++
case P.L.	+	+
Niemann-Pick disease type B		
late infant. var. ($n=1$)	+/++	+/++
adult variant ($n=1$)	+/+	−/+
Niemann-Pick disease type A		
case 1 (8 yr)	+/++	+/++
case 2 (5 yr)	−/+	++
case 3 (6 yr)	+/++	+/++

* semiquantitative evaluation of LP and other lysosomal storage phenomena is given in Table 1

cases). In other cases it was a prominent finding, for example in two siblings with fatal cholestatic hepatopathy, and in four cases with primary storage splenomegaly, splenectomized because of hypersplenism (4 cases, see Elleder 1989).

No lipid storage could be demonstrated in SSE using lipid histochemistry and electron microscopy. In nine cases there was significantly increased deposition of LP with tinction and ultrastructure identical with that in the thrombocytopaenia group. The amounts varied around the 1+ value (Table 1). Maximum accumulation (Fig. 1 b) was found in two siblings with a fatal cholestatic disease strongly resembling Byler's disease (Clayton et al. 1969). The amount of ceroid in red pulp foamy histiocytes was minimal. In these two cases and in several others where unfixed tissue was available for enzyme histochemistry, the acid phosphatase activity displayed a clear-cut increase in the SSE, without alkaline phosphatase activity induction.

In the group of inherited lysosomal enzymopathies (27 cases) the lysosomal LP accretions were a frequent finding. They were found either as the sole manifestation of the lysosomal disorder (Table 1) in the form of unspecific LP granules (see above) or in combination with disease specific storage phenomena (Table 2). When in combination, there were two patterns of LP deposition. In the first, LP was either deposited on the periphery of the storage lysosomes, as typically seen in sphingomyelinase deficiency where it was composed of a layer of densely packed membranes (about 150 nm thick) with a period about 7.8–9.2 nm, contrasting with the lucency of the rest of the lipid storing lysosomal interior. This pattern was a feature of two cases with prolonged course (aged 6 and 8). In the youngest patient (aged 5) the LP layer was rudimentary. In two adult cases of sphingomyelinase deficiency type B the bulk of the lysosomes were occupied by LP mass the rest displayed combined lipid-LP storage again with LP deposition along the limiting membrane. The second pattern was seen in two other entities displaying concomitant LP-lipid storage, Niemann-Pick type C and Fabry's disease (Table 2). The LP mass with pleiomorphic ultrastructure was randomly mixed with the stored lipid membranes. The staining of LP was typical, but sudanophilia was much stronger than in the preceding groups especially in cases of mixed lipid/LP storage.

In the group of neuronal ceroid – lipofuscinoses (11 cases) the degree of SSE involvement did not exceed the degree seen in the previous groups (Table 1). The ultrastructure of the deposited lipopigment retained the fine structural pattern pertinent to the corresponding NCL subvariant (reviewed in Zeman and Siakotos 1973), with the exception of one case with remarkably pleiomorphic lysosomal deposits.

Discussion

The results point to a hitherto undescribed tendency of SSE to produce residual bodies of LP type. With the

exception of one observation (Zvi and Lampert 1986), I have been unable to find any other reference to SSE lipopigmentation except perhaps for "colourless granules or droplets in the venous and sinus endothelium" described occasionally (Jordan and Speidel 1931; Lennert 1950). In protracted types of sphingomyelinase deficiency Lake (1983) described deposition of autofluorescent storage products in SSE.

In our control series the process of LP deposition in SSE showed no age-dependence. It was expressed in pathological conditions the common denominator of which was an increased demand on the lysosomal system, which could be inferred from the concomitant lysosomal overload in pulpal histiocytes. Oddly enough, the SSE lysosomal system reacted solely by a reactive progressive LP deposition without any recognizable accumulation of a lipid precursor in many instances. With the exception of age-independence the process resembled that leading to lipofuscin generation where denatured proteins are reputed to be the main building stone (Davies 1988). In this feature SSE differs fundamentally from histiocytes, where the ceroid LP variant predominates, dependant on endocytosis and derived from endocytosed lipid rich structures (Gedigk and Totovic 1983; Jolly et al. 1989).

In some of the lysosomal enzymopathies the LP generation in SSE is based on a mechanism different from that mentioned above. It occurs inside the preexisting lipid storing lysosomes as a concomitant phenomenon representing either an additional lysosomal lesion or a direct origin from the stored lipid or other substance simultaneously present in lysosomes.

An interesting feature is the absence of alkaline phosphatase induction in SSE even in states of excessive LP production. In this LP storage contrasts with classical enzyme substrate storage either of lipid or mucopolysaccharide series in which alkaline phosphatase induction has been described (Elleder 1979b).

It is difficult to say to what extent the LP deposition property is unique to the endothelium in general. Sporadic endothelial lipofuscin is a frequent finding (unpublished observations). Hemidense variant LP was repeatedly found in larger quantities in the liver sinusoids in sphingomyelinase deficiency (Elleder et al. 1980). A remarkably high degree of LP deposition was found in the lymph node sinuses where they are known as Hamazaki's or Hamazaki's-Wessenberg's bodies (Hamazaki 1938; Sieracki and Fisher 1973). They are mostly found in histiocytes; their relation to the sinus endothelium is unknown.

All the above characteristics show that SSE is different from the pulpar histiocytes. It has a lack of phagocytic activity demonstrated in a series of experiments (Burke and Simon 1970; Cotran 1965; Cotran et al. 1965; Florey 1967; Moore et al. 1961; Nanney et al. 1984; Snodgrass 1968; Wennberg and Weiss 1967). The same conclusion can be drawn from results of reports on splenic changes in various spontaneous disorders having an increased lysosomal load as a common denominator (Bernick and Patek 1961; Ferrans et al. 1971; Ishihara et al. 1984; Roberts et al. 1970). The only exception seems to be the relatively high degree of lysosomal induction by iron overload. This may be caused by an exceptionally high concentration of transferin receptors in SSE (Buckley et al. 1985).

The further point of difference between SSE and pulpar histiocytes is the storage pattern in lysosomal enzymopathies. Thus, in Gaucher's disease, the storage manifestation based on haemophagocytosis (Brady and Barranger 1983) the SSE is entirely normal thus contrasting starkly with pulpar storage histiocytes. In the mucopolysaccharidoses, at least in some types, SSE clearly predominates in the quantity of storage over histiocytes (Wolfe et al. 1964) which might reflect an ability for plasma glycosaminoglycans degradation as described in the rat liver sinusoids (Smedsrod et al. 1985). The conspicuous storage in SSE in Fabbry's disease is again in accordance with the prominent tendency of the endothelium to store in this disease (Desnick and Sweeley 1983). Reports on SSE storage in other lysosomal enzymopathies are still rare (Alroy et al. 1984; Lake 1983; Martin et al. 1984; O'Neil et al. 1978) and the topic should attract more interest in the future.

The last point of difference from histiocytes is the enzyme equipment of SSE, namely low activities of lysosomal enzymes (Dorfman 1961; Stutte 1968), the presence of dipeptidylpeptidase IV activity (Elleder 1979a), and the possibility of alkaline phosphatase induction (Elleder 1979b). Nonspecific esterase activity, often given as an argument for the histiocytic nature of SSE, never reaches the intensity seen in the endothelial cells of the lymph node epitheloid venules (Lennert 1978). The coexpression by SSE of one of the monocyte antigens is not helpful in defining their cell type as they share antigens even with some T lymphocyte subsets (Buckley et al. 1985).

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