Pathol. Oncol. Res. (2008) 14:205–208
DOI 10.1007/s12253-008-9048-6

ORIGINAL PAPER

Microscopic Peliosis of Pancreatic Islets Associated with Thrombotic Thrombocytopenic Purpura

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Received: 25 March 2008 / Accepted: 1 April 2008 / Published online: 23 April 2008

Abstract Peliosis is a rarely seen histological finding with unexplained fully etiology and pathogenesis. It is presented as cyst-like blood filled cavities. The presence of peliosis in the endocrine part of the pancreas is extremely rarely reported microscopic phenomenon. The authors provide histological, histochemical, immunohistochemical and ultrastructural investigation of microscopic peliosis in the pancreas from an autopsy case with thrombotic trombocytopenic purpura. The findings give ideas for a wide range of pathophysiological and morphogenetic comments of such an unusual morphologic presentation.

Keywords Disseminated intravascular coagulation, pancreas · Peliosis · Pancreatic islets · Thrombocytic thrombocytopenic purpura

Introduction

Peliosis (P) is a morphological phenomenon, characterized by the presence of blood-filled cavities separated by incomplete endothelium in the microcirculation of internal organs [1–5]. The most frequent localization is in liver and spleen [2, 5–9], and less frequently seen in kidneys, suprarenal glands, bone marrow, lymph nodes, gastrointestinal tract, pituitary gland, lung [2, 4, 7, 10–12].

The involvement of Langerhans islets is extremely rare. To our best knowledge, there are only three cases in the literature associated with adenomas of the endocrine part of the pancreas—the two in a patients with multiple endocrine neoplasia (MEN-1) [2, 13], and the third one is in a case with metastatic prostatic cancer [14]. The pathologic findings of P in pancreatic islets associated with thrombocytic thrombocytopenic purpura (TTP) are presented.

Case Report

A 60-year-old woman with a previous viral infection symptomatically treated at home was admitted at the clinic of neurology, affiliation of our university hospital due to localized ischemic brain infarction. In due course of treatment, hemolytic anemia and thrombocytopenia appear for which she was consulted by hematologists. General status of the patient was severely injured, temperature fluctuated, an icteric colour of skin and mucosal surfaces became evident, hemorrhagic rash measuring 3–4 cm in diameter soon appeared on the lower limbs. Spleen, liver and lymph nodes were unremarkable. No cardiac manifestations became present, renal examination was normal. From laboratory: RBC—1.8; 2.5×10^{12}; Hb—54, 65.78 g/l ; HCT—0.15, 0.24; WBC—15.3, 11.8×10^{9}; PLT—16, 27, 16×10^{9}; red blood cell precipitation velocity—67, 38, 58 mm/h; RET—63‰, 153‰; T BIL—68, 57, 148 μmol/l (at the beginning indirect followed by direct hyperbilirubinemia); UREA—13, 23.6 mmol/l; UR AC—535 μmol/l; LDH—2,943, 2,770 U/I; fibrinogen—3.4, 3.6 g/l; TT—29, 30 s; PT—50%, 47%; fibrin degradation products (slightly elevated.)—1.0 μg/ml. Urine–urobilinogen—increased, bilirubin—+, hemoglobin—+;

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sediment—red blood cells, leukocytes, casts, urates; proteinuria—5, 44 g/l Cerebral computer-axial tomography revealed hypodense lesion in left cortical area. Clinical diagnosis of TTP complicated with ischemic brain infarction. The disease has most probably developed as a result of previous infection or another unknown toxic reason. Despite the complex therapy—corticosteroids (2 mg/kg body mass for 6 days), blood products infusion, Nootropil, symptomatic medications, pulmonary edema developed as a complication along with hepato-renal syndrome, shortly afterwards the patient dropped into a coma and died from cardio-vascular arrest.

Materials and Methods

The tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Four-micrometer-thick sections from the paraffin blocks were stained with hematoxylin–eosin (HE), periodic acid+Schiff reactive (PAS), Gomori silver impregnation and Mallory's fibrin stain.

Stains for factor VIII (von Willebrand—polyclonal rabbit antihuman, ready-to-use, Dako Glostrup, Denmark) and CD 34 (monoclonal mouse antihuman dilution 1:50, Dako, Glostrup, Denmark) was performed applying immunoperoxidase method. Visualization with DAB and counterstaining with Meyer's hematoxylin followed.

For electron microscopy, several small pieces from pancreas after 24-h bathing in distilled water, were fixed in 2.5% glutaraldehyde, osmicated, dehydrated in graded ethanol, processed through propylene oxide and embedded in Durcopan; semi-thin sections were stained with toluidine blue, appropriate areas were selected under light microscope for ultra structural study. Ultra thin sections were stained with uranyl acetate–lead citrate and investigated under transmission electron microscope (Philips CM 12 /STEM).

Results

At autopsy, the main macroscopic findings included jaundice of the skin and mucosa and small petechiae on skin, mucosal and serosal surfaces; an infarction measuring 1.5 cm in diameter was grossly visible in the left parietal hemisphere in a stage of early organization. The bone marrow was red and hyperplastic. The pancreas showed no gross morphological changes. No tumor was identified into the viscera.

Histology revealed platelet micro thrombi in central nervous system, myocardium, lungs, glomerular capillaries, stomach, pancreas; micro hemorrhagic skin spots, focal necrosis in internal organs.

Blood-filled cavities were easily identified in more than 60% of the islets of the pancreas (Fig. 1a). Some were filled with red blood cells, others contained only stagnated plasma into their lumens or were found empty. Insular and peri-insular blood vessels were plugged with thrombotic occlusions (Fig. 1b). Dilated blood spaces were partially bordered by PAS (data not shown) and Gomori-positive fibers (Fig. 1c) with interior incomplete endothelial and endocrine cell lining. Exocrine pancreas showed focal ischemic necrosis and areas with lipomatosis.

Immunohistochemistry revealed that most of the endothelial cells covering these dilated loops and part of the micro thrombi were CD 34 positive (Fig. 1d). Both plasma and microthrombi in the blood filled cavities were strongly positive for factor VII (Fig. 1e).

Ultrastructurally, dilated blood spaces were separated by fenestrated endothelial cells with focal blebs. The cytoplasm of the endothelial cells contained vacuoles but no ruptures nor red blood cell migration were noticed. The cellular nuclei were elongated by shape with predominant heterochromatin. Few erythrocytes were visible (Fig. 1f).

Discussion

Etiology and pathogenesis of P are still under debate. This peculiar microcirculatory phenomenon is mostly seen in liver and spleen, where hormonal stimuli (estrogen), post therapy effect from steroids and anabolic substances, contraceptive pills, tumors, debilitating diseases such as tuberculosis, chronic inflammatory diseases are involved [1, 2, 9, 14]. P in the aforementioned organs and into the lymph nodes is described in immunosuppression, including HIV infection [7]. Other rare localizations of P have been observed in kidneys of patients on chronic dialysis, in heart after cardiac transplantation [2], in ectopic pituitary adenoma located in the sphenoid sinus [14], in lungs [12], bone marrow, suprarenal and gastrointestinal tract [2].

There are only three cases in the literature presenting microscopic P in the pancreatic islets: the first two in a patient with MEN (multiple adenomas of the islets and concomitant adenoma of the pituitary, and pancreatic adenomas and carcinoma) [2, 13] and the second case is in a 58-old-year male with acinary type of prostate adenocarcinoma with bone metastasis who died from multiple cerebral and subendocardial infarcts, but at autopsy there was an incidental finding of a pancreatic adenoma [14].

Peliosis in the pancreatic islets in our case has no association with any malignancy nor pancreatic islet adenoma. The corticosteroid therapy is a very short one—lasting 6 days only. Consequently, any pathogenic consid-

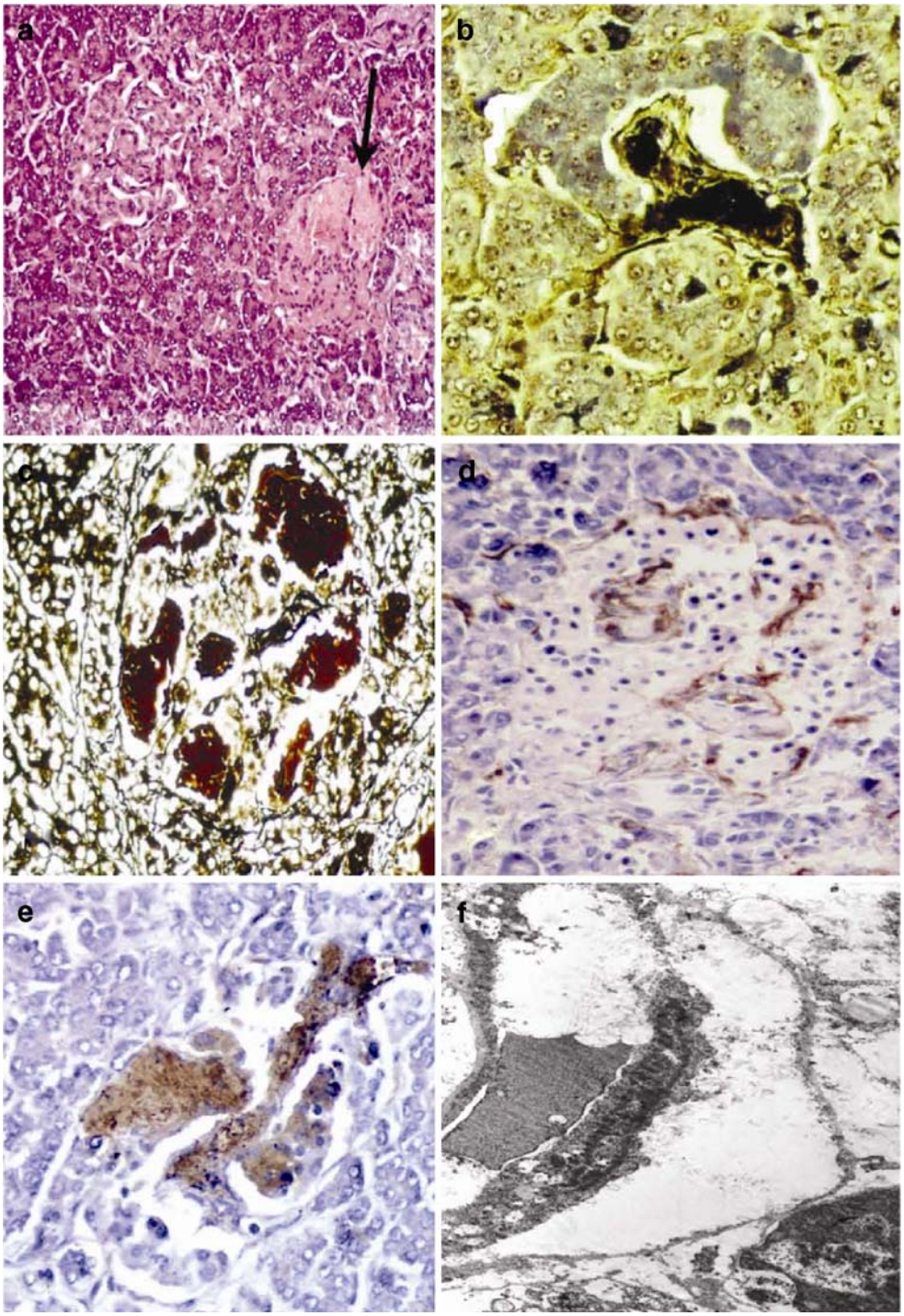

Fig. 1 Dilated blood-filled cavities in Langerhans islets (**a**, *arrow*) containing microthrombi (**b**), surrounded by incomplete reticulin fiber network (**c**) and endothelium (**d**) ; stagnated plasma in the blood-filled spaces is strongly positive to factor VIII (**e**). Ultrastructure **f** cystically transformed capillary covered with fenestrated endothelium with an erythrocyte into the lumen (**a** hematoxylin–eosin, original magnification ×60 ; **b** Mallory's fibrin, original magnification ×100 ; **c** Gomori silver impregnation, original magnification ×200; **d** immunoperoxidase staining for CD34, original magnification ×400 ; **e** immunoperoxidase staining for factor VIII, original magnification ×400 ; **f** electron microscopy, original magnification ×5,750)

eration with tumor or hormonal stimulus and subsequent induction of peliosis is non contributory.

We speculate that the origin of peliosis in our case is associated with a pathogenic mechanisms involved in the onset of TTP. TTP is a microcirculatory disorder with a multiorgan involvement. Major role in its pathogenesis is exerted by plasma metalloproteinases—ADAMTS 13 which in normal conditions digest factor VIII into small non thrombogenic particles [15]. The decrease of the enzyme or its total absence leads to the formation of multiple micro thrombi composed predominantly of platelets in the microcirculation of internal organs—mainly brain, kidney, heart, pancreas and suprarenal glands. Impaired venous drainage in TTP is presumably secondary to activation of coagulation. Laboratory findings and immunohistochemical reactivity for factor VIII and CD 34—two proteins that participate in the process of coagulation [16, 17] are in proof of that.

Impaired venous drainage is pointed as a pathogenic factor in the appearance of P both in ectopic adenoma of the anterior pituitary [11] and idiopathic portal hypertension [3]. It is tempting to speculate that micro thrombi seriously impair venous drainage and apart from angioneurotic, paretic and ischemic changes, they contribute to dilatation of the blood vessels and P [18].

Our case with TTP supports the concept that stimulated intravascular coagulation with subsequent thrombogenesis plays a major role in the appearance of peliosis. Activated local coagulation is supposed to participate in the pathogenesis of the other previously reported cases with P—in tumors (both adenomas and carcinomas) as paraneoplastic effect, as association in hematological malignancies and in drugs and toxins sinusoidal wall damage.

Predominance of P in some organs is explained with the normal anatomic structure of the blood vessel walls of the most commonly affected organs and the specificity of their microcirculation. In liver, spleen and lymph nodes, microcirculation is of sinusoidal type. Lack of basement membrane makes vessel walls extremely vulnerable to different toxins especially for the fenestrated capillaries in suprarenal glands, glomeruli, anterior of the pituitary and pancreatic islets. In these organs, the circulation is of portal type which facilitates the secretion of peptides in the capillaries. P is probably 'comfortably suited' in organs with such specific microcirculation.

Peliosis in TTP assumes a new causative mechanism for its development. Current views focus on deficit in ADAMTS 13 inactivated by auto antibodies against the enzyme [19]. Immune factors similar to the circulating immunoglobulins in Waldenstrom macroglobulinemia [20] triggered by infectious or toxic molecules at the onset of the disease, can lead to activated coagulation and subsequent circulatory complications including peliosis.

In conclusion, our case is the first description of pancreatic islets peliosis in association with TTP as a confirmation of the hypothesis of Tsokos and Erbersdobler [4] for the heterogeneity of clinical settings in which P develops.

The present case emphasizes two problems:

1 a new probable mechanism in the pathogenesis of P-activated systemic or local coagulation;
2 an additional but substantial etiological factor for the appearance of P-alterated immune function.

This case supports the relationship between TTP and P. The latter can be added as infrequent and 'exotic' histopathologic feature associated with the disease.

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