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Gastrointestinal and Pancreatic Involvement in Mediterranean Spotted Fever Fatal Cases

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Mediterranean spotted fever (MSF) is a rickettsial disease, caused by *Ricketsia conorii*. It is a tick-borne infection endemic for several regions in Bulgaria along the Maritza River and the Black Sea coast. The characteristic features of MSF include a skin eschar (tache noite) at the site of tick bite, fever, flu-like symptoms and maculopapular rash spread on the body and extremities, not sparing the palms and feet. MSF has usually mild or moderate course, however severe, so-called "malignant" forms have been observed with involvement of vital organ systems and lethal outcome. We present two rare and fatal complications of MSF – gastrointestinal bleeding and pancreatic steatonecrosis. In both cases the organ involvement had histomorphological confirmation at autopsy. MSF diagnosis was confirmed serologically by an indirect immunofluorescent assay. Awareness of the possibility of gastrointestinal bleeding and necrotizing pancreatitis in MSF patients is essential to professionals for conducting a convenient behaviour and help.

Key words: Mediterranean spotted fever, fatal complications, gastrointestinal bleeding, necrotizing pancreatitis, histomorphology

Introduction

Mediterranean spotted fever (MSF) is caused by *Ricketsia conorii*. It is a tick-borne rickettsial infection endemic for several regions in Bulgaria along the Maritza River and the Black Sea coast. The life cycle of rickettsiae involves insect vector – *Ripicephalus sanguineus*, and mammal reservoirs – mainly domestic and stray dogs. Humans are accidental hosts. The main clinical signs and symptoms of MSF include a skin eschar (tache noite) at the site of tick bite, fever, flu-like symptoms and maculopapular rash spread on the body and extremities, not sparing the palms and feet. MSF has usually mild or moderate course and had long been considered a benign disease, however the so-called "malignant" forms have been observed with involvement of vital organ systems and lethal outcome [1, 8]. A hallmark of MSF pathology is the rickettsial vasculitis.

Gastrointestinal system is involved in the disseminated rickettsiosis with perivascular lymphohistiocytic infiltrates in tela submucosa and tunica muscularis of the organs' wall. Submucosal vasculitis can lead to mucosal erosions, ulcers, petechiae or hemorrhage. The pancreatic gland involvement in rickettsial vasculitis ranges from catarrhal to hemorrhagic-necrotizing pancreatitis [2, 4]. The mentioned MSF complications are almost unknown among patients and health professionals especially in non-endemic regions of Bulgaria similarly the imported rickettsioses in non-endemic countries. The purpose of this communication is to make the medical community aware of the possibility of gastrointestinal hemorrhage and concomitant necrotizing pancreatitis in the most severe, often fatal forms of MSF.

Patients and Methods

We present two rare and fatal complications of Mediterranean spotted fever – gastrointestinal bleeding and acute necrotizing pancreatitis. The organ involvement had histomorphological confirmation at autopsy. We conducted a histopathological study including complete post-mortem examinations of the specimens of liver, lung, kidneys, stomach, pancreas and brain. The samples were fixed in 4% neutral buffered solution of formaldehyde, embedded in paraffin, sectioned at 5 μm thicknesses, and processed by staining with hematoxylin/eosin for evaluation of histopathology. The MSF diagnosis was confirmed by an indirect fluorescent antibody assay, with IgG ≥128 and/or IgM ≥64 being considered indicative of acute infection.

Ethical consideration: Informed autopsy consent was signed by the relatives of the deceased patient. The case we described is completely anonymous and the histological examination of autopsy samples did not reveal its identity.

Results

In our previous research we investigated 55 patients with a very severe, so called "malignant" form of MSF named "MSF form with multiple organ involvement". Gastrointestinal system was involved in 8 of these patients and 6 of them were lethal [1]. Here we present the clinical characteristic and histomorphological data of one of the deceased patients with involvement of the digestive tract (gastrointestinal system and pancreatic gland) in the rickettsial infection.

Case description: A 61-year-old woman, with a previous history of long-standing diabetes mellitus type 2, had a seven-day history of fever (39.5˚C), chills, headache, vomiting and myalgia. She had contacts with her pet dog. On day 4 after the onset of symptoms, a rash appeared on her body and limbs. Within two days, her condition deteriorated severely. She was admitted to the hospital intensive care facility in the state of shock – in circulatory collapse, sweating, with thready rapid pulse, pale skin and mucous membranes. She was confused and hypoactive. There was an abundant maculopapular and hemorrhagic rash on the body and limbs, hands and feet, and an eschar (tache noire) under the left scapula. Melena and hematemesis appeared on the second day of admission. Erosive gastritis was diagnosed on upper endoscopy. Ulcers were not detected. Despite the complex resuscitation efforts exitus letalis occurred 34 h after admission. The serology was positive for *Rickettsia conorii*.

Autopsy protocol: Generalized thrombo-vasculitis with perivascular lympho-histiocytic infiltration; multiple petechial hemorrhages on all mucous and serous

membranes; three acute ulcers in the stomach fundus with massive bleeding in the digestive tract; acute post-hemorrhage anemia; acute pancreatic steatonecrosis; focal interstitial nephritis with thrombotic vasculitis of the renal microcirculation; brain edema and pulmonary edema.

Microphotographs of histopathological changes in the gastric mucosa serve as illustrations of the presented case (**Fig. 1; Fig. 2**). At the same time, we present microphotographs of catarrhal gastritis with inflammatory perivascular infiltrates in a patient who died from other MSF complications, thus highlighting the different extent of the gastric mucosa involvement in the rickettsial vasculitis. (**Fig. 3; Fig. 4**).

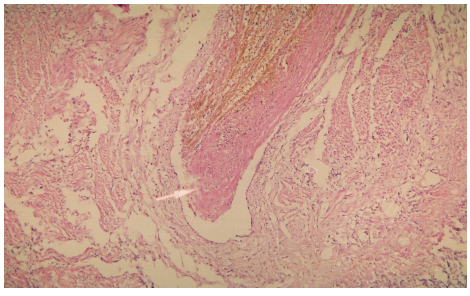

Fig. 1. Bottom of an acute ulcer. Gastric wall mixed thrombus in an arteriole (arrow). (Hematoxylin-Eosin, ×200)

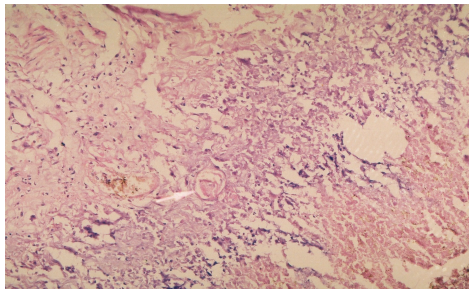

Fig. 2. Gastric mucosa with hemorrhage and necrosis; hyaline thrombus at the base (arrow). (Hematoxylin-Eosin, ×200)

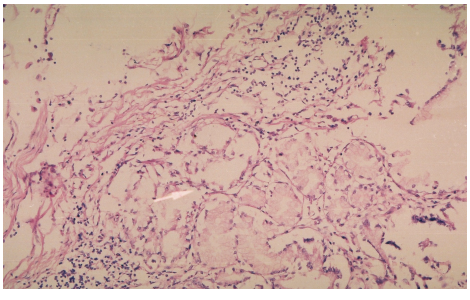

Fig. 3. Gastric wall. Relatively preserved gastric mucosa. Catarrhal gastritis with perivascular round cell infiltrates (arrow)
(Hematoxylin-Eosin, ×200)

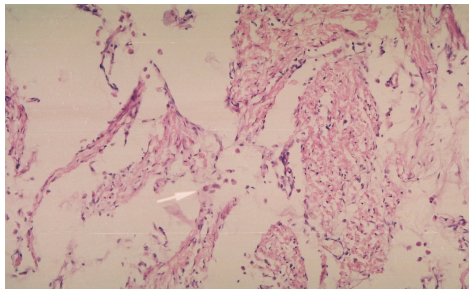

Fig. 4. Gastric wall with edema and inflammatory infiltrate of lymphocytes and plasma cells (arrow)
(Hematoxylin-Eosin, ×200)

Pancreatic involvement in the MSF rickettsial vasculitis is not a common event. Our previous investigation showed that among 55 patients with malignant MSF cases the pancreatic gland was involved in 5 patients and 4 of them died [1]. In an attempt to demonstrate the different amplitude of pancreatic involvement in the rickettsial microvascular injury we present a microphotograph of the pancreatic gland preserved structure in a patient who died from other MSF complications (**Fig. 5**) and a microphotograph of pancreas lytic steatonecrosis in the patient we described above (**Fig. 6**).

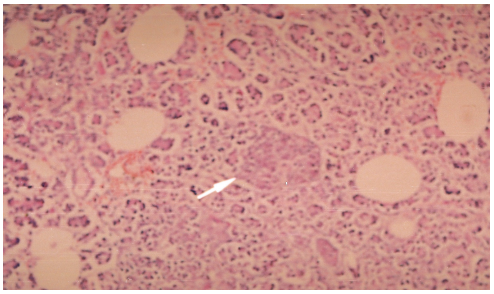

Fig. 5. Pancreas. Centrally located Langerhans island (arrow); around – exocrine part of the gland. (Hematoxylin-Eosin, ×200)

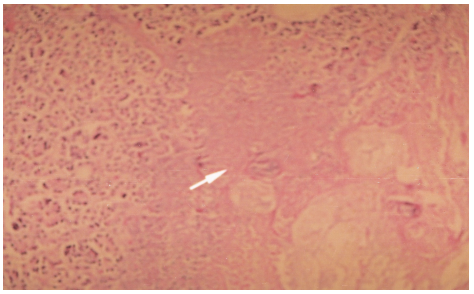

Fig 6. Pancreas Lytic necrosis (steatonecrosis) (arrow)
(Hematoxylin-Eosin, ×200)

Discussion

The most likely pathophysiological mechanisms of the organ involvement in rickettsioses seem to be the increased vascular permeability, caused by numerous closely spaced foci of endothelial cell damages in the microcirculatory system [12]. The major observed pathological lesions in rickettsial diseases consist in vascular and perivascular mononuclear cell-rich inflammatory foci with or without thrombosis and necrotic hemorrhages [4].

Mediterranean spotted fever is a rickettsial disease that affects multiple organs due to the widespread microvascular damage. Submucosal and muscularis perivascular lymphohistiocytic infiltrates and vasculitis are the most frequent findings in the stomach. Mucosa is involved only secondary in the underlying vascular lesions resulting in mucosal petechiae, erosions, ulcers and hemorrhage. Hemorrhages in the gastrointestinal tract are severe, although uncommon complication of vasculitic changes in malignant forms of MSF. In a study by Ruiz-Beltrán et al. bleeding appeared as a consequence of multiple acute superficial erosions of the gastric mucosa. The histological substrate for these lesions was identified as a lymphohistiocytic vasculitic process affecting the small vessels of the gastric wall [10]. Erosions and several ulcers in the gastric wall of MSF patients have been reported by other authors as well [6]. Vascular inflammation, capillaritis, or lymphohistiocytic vasculitis like those in a whole gastrointestinal tract with or without vascular dilation and endothelial cell swelling was identified in esophageal and intestinal lesions, though infrequent and vascular injuries were moderate only [4]. Similarly, in some MSF fatal cases because of crucial organ involvement, we found moderately expressed scattered lymphohistiocytic perivascular infiltrates in the gastric mucosa referred as a catarrhal gastritis thus highlighting the different range of gastric mucosa involvement in the rickettsial vasculitis.

Acute necrotizing pancreatitis is characterized by necrosis in and around the pancreas. It is subdivided anatomically into parenchymal, peripancreatic, and combined subtypes, depending on whether it involves pancreatic parenchyma only, or peripancreatic tissues with the peripancreatic fat, or both [3, 11]. Pancreatic involvement in MSF appears to be less frequent than gastrointestinal involvement and has been rarely reported in literature [5, 9, 12]. In this report we present a case of gastrointestinal bleeding with concomitant pancreatic steatonecrosis considering both lesions related to a common cause – rickettsial microvascular damage. However, we have also described hemorrhagic-necrotizing pancreatitis and pancreatic fat necrosis in MSF patients

without gastrointestinal hemorrhage [2], suggesting that the observed phenomena are not necessarily related and interdependent.

Existing opinions suggest that although the pancreatic interlobular vasculature is a frequent site of perivascular lymphohistiocytic infiltrates, the lesions in MSF are small and scattered; vasculitis with endothelial cell damage is much less frequent and its contribution to the clinical picture is uncertain [4]. According to some reports, however, rickettsial vascular injury of the pancreas occurred frequently, although the parenchymal lesions might not be severe enough to qualify as pancreatitis [7]. In one of the cases reported in the literature, the pancreatic involvement was mild, with a prompt response to antibiotic therapy [5]. Other report, however, announced a serious multiorgan involvement, including the pancreas in South African tick bite fever (*R.conorii)* patients with 2 fatal cases. Immunofluorescent organisms of *R.conorii* were demonstrated in vascular endothelium of pancreatic septa [12].

Conclusion

Awareness of the possibility of gastrointestinal bleeding and necrotizing pancreatitis in MSF patients is essential to the critical care of professionals for conducting prompt practical management and providing an appropriate treatment.

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