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## Case Report

# Salmonella sepsis in a patient with TLR4 gene polymorphisms<sup>☆</sup>

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### ABSTRACT

Non-typhoid Salmonella gastroenteritis is one of the most common forms of intestinal infections among the population of developed countries and generalized forms of infection are rare. We present a case of 67-year-old woman with salmonella sepsis, deep venous thrombosis, and septic thromboembolism of pulmonary artery complicated with development of necrotizing pneumonia. Generalization of the infectious process was mediated by the presence of polymorphisms in the TLR4 gene. Development of pulmonary infarction is infrequent. Even rarer is a formation of cavities in infarcted lung tissue, usually in the background of the infectious disease. A combination of 2 rare conditions in 1 patient demonstrates the need of multidisciplinary approach in treatment of severe and atypical forms of infectious diseases to evaluate the primary etiology of such state. The article will discuss various aspects of lung tissue damage caused by Salmonella and give a brief overview of the literature on this topic.

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## Introduction

Non-typhoid Salmonella gastroenteritis is one of the most common forms of intestinal infections among the population of developed countries. Non-typhoid Salmonella can cause both local forms of infection and generalized – typhoid and septicemic – forms of disease. The latter is Salmonella sepsis. However, generalized forms are not common, only in 5%

10% of cases, mainly among immunocompromised patients. In septicemic salmonellosis, the most common infected foci are gastrointestinal tract, pericardium, endothelium of blood vessels, meninges, bones, and joints [1–4].

Salmonella are intracellular pathogens, gram-negative bacteria that, when they invade epithelial cells, induce the process of Th1-mediated immunity. In this type of inflammatory response, antigen-presenting (dendritic) cells trigger the differentiation of naive Th0 lymphocytes into Th1

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lymphocytes. The latter, in turn, interact with macrophages, which in this case, are the main effector cells. Adequate development of cell-induced inflammation is regulated by several receptor complexes and cytokines. One of the main is a receptor recognizing lipopolysaccharide (LPS) of the bacteria – toll-like receptor 4 (TLR4) specifically. A defect in one of these connected elements entails changes in the cell numbers, receptors' structure and cytokine concentrations, which can lead to generalization of the infectious process [5,6].

We present a clinical case of a patient with Salmonella sepsis, developed on the background of the presence of polymorphisms in TLR4 gene.

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## Clinical case

Woman N., a 67-year-old, complaining on fever up to 40°C, shaking chills, shortness of breath at rest, pressure drop to 90/60 mm Hg was hospitalized in the intensive care unit. She became acutely ill 12 days ago, when she had aching pain in the epigastrium, seedy light-yellow stool up to 4-5 times a day, and subfebrile fever. She was on self-medication – she took intestinal sorbents, metronidazole with a positive effect in the form of normalization of the stool, disappearance of epigastric pain and the temperature returned to normal. On the third day, from the beginning of the disease her right lower leg got swollen and painful. Two days later, while going upstairs, she suddenly developed shortness of breath, retrosternal discomfort. Some hours later her state worsened with developing of dry cough, febrile fever, spread and strengthening of the chest pain and aggravation of the dyspnea.

It is known that for the last 2 months she was living in private house in the suburb with relatives (they have no signs of infectious and inflammatory diseases within 2). She almost daily consumed heat-treated eggs, milk, cottage cheese bought from the farmers. Previously she had duodenal ulcer (the last exacerbation was 10 years ago, she continues the course of gastroprotectors). Only relevant family history was maternal exposure to typhoid fever.

At the time of hospitalization patient was tachypneic, tachycardic and hypotensive, with a high grade fever. The right lower leg was swollen and painful. No peripheral lymphadenopathy has been detected.

According to simplified Wells and Geneva score criteria, the patient has a high probability of pulmonary embolism (PE) [7,8]. CT angiography of the chest organs was performed (Figs. 1, 2).

The examination confirmed the presence of a massive pulmonary embolism of the right branch of the pulmonary artery, against which it was impossible to exclude thromboembolism of smaller branches in this territory. The presence of infarct pneumonia in S1-2 of the right lung was established, represented by areas of consolidation of the lung tissue of a triangular shape, linear subsegmental atelectasis in S3 of the right lung. Also, a destruction cavity was found in the S1 of the right lung, draining into the segmental bronchus and partially filled with liquid contents.

During echocardiography, there was a slight dilatation of the right ventricle, signs of pulmonary hypertension (mean systolic pressure in the pulmonary artery was 37 mm Hg).

Duplex scanning of lower limb veins revealed a floating deep vein thrombus of the right lower limb with the upper border of the thrombus at the level of the common femoral vein.

Blood tests proved the course of an infectious process, revealed normocytic normochromic anemia and marked hypercoagulation state.

Microbiological examination of blood revealed the growth of D group Salmonella (negative Vi antigen), microbiological examination of sputum found D group Salmonella 10<sup>5</sup> CFU/mL, *Candida alb.* 10<sup>2</sup> CFU/mL.

The stool culture on the intestinal group was negative.

Summarizing all clinical data the patient had septicemic variant of salmonellosis (group D Salmonella, negative Vi antigen), complicated with deep vein thrombosis of the right lower limb, massive pulmonary embolism community-acquired destructive pneumonia.

On the fifth day from the beginning of pathogenic and symptomatic therapy, although there was mild improvement in patient's state overall significant swelling and pain of the right lower leg preserved, a repeated duplex scan of the veins of the lower limbs showed growth of the thrombus and development of acute ascending thrombophlebitis. Microbiological examination of the thrombus, conducted after Trendelenburg's operation revealed the growth of group D Salmonella (negative Vi antigen).

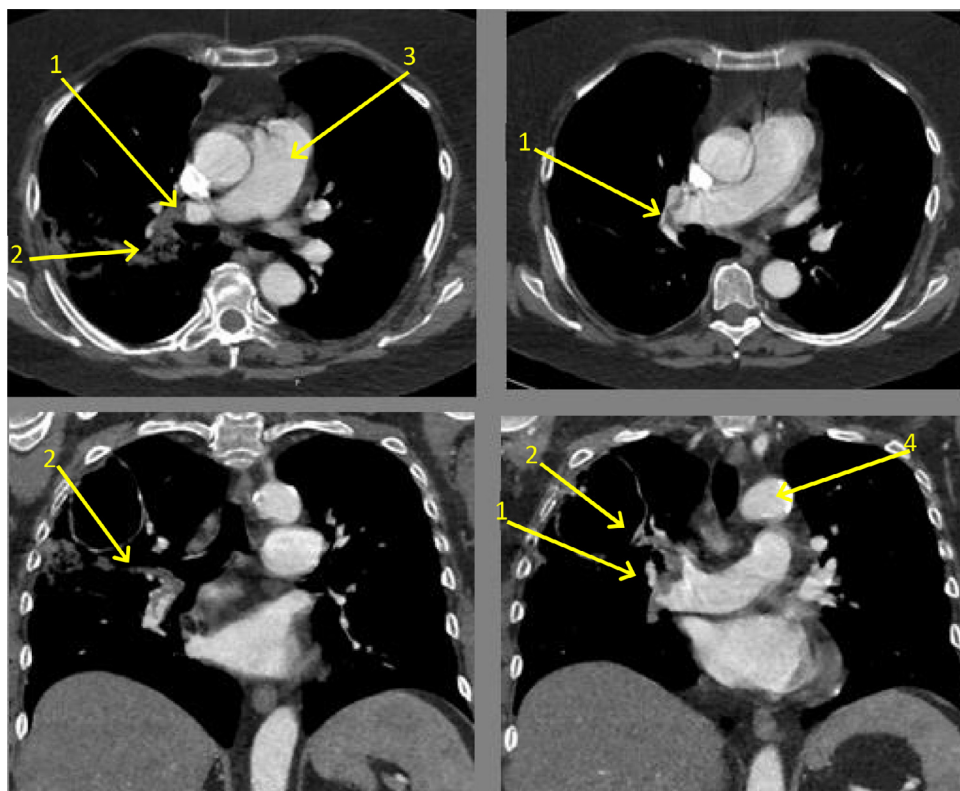
Repeated chest CT (Fig. 3) also demonstrated negative dynamics. Cavities with liquid content against the consolidated lung tissue in S2-S3 of the right lung and small pleural effusion was revealed.

Withal there was noted a diameter diminishing of the cavity in S1 of the right lung and a reduction of necrotic debris inside it.

Therapeutic strategy was changed immediately and the treatment was continued for the next three weeks. When a control chest CT was performed, it revealed significant positive dynamics. The patient was discharged 4 weeks after hospitalization, without antibiotic therapy

Chest CT performed 3 months later showed absence of infiltrative and destructive changes in the lungs. CT angiography showed complete lysis of the thrombus in the branches of the right pulmonary artery (Fig. 4).

Since the patient developed severe generalized Salmonella infection, had no risk factors in the past medical history (immune deficiency, oncological diseases, chemotherapy) and had family history of typhoid fever, a presence of latent cellular immunity pathology was suggested. The patient was genotyped for the presence of cosegregating single nucleotide polymorphisms in the TLR4 gene (Asp299Gly and Thr399Ile) by pyrosequencing using the genetic analysis system "PyroMark Q24" ("Qiagen", Germany). G allele in a heterozygous state of the Asp299Gly polymorphism (896A/G rs4986790) and T allele in the heterozygous state of the Thr399Ile polymorphism (1196C/T rs4986791) have been identified, which are associated with reduced sensitivity to LPS of bacteria and are associated with susceptibility to gram-negative severe infections [5]. According to the 1000 Genomes project, the frequency of the



**Fig. 1** – CT angiography at the admission. At the level of bifurcation of the right pulmonary artery, a saddle-shaped thrombus (1) is determined, spreading into the branches of the upper lobe (2). The pulmonary trunk (3) is slightly expanded (diameter is 32 mm), the right and left branches of the pulmonary artery are not expanded (diameters are 24 and 21 mm, respectively). Aortic walls are calcified (4)

A/G genotype in the Asp299Gly polymorphism in the global population is 10.9%, and the frequency of the C/T genotype in the Thr399Ile polymorphism is 7.4%. Frequencies in the European population are 7.4% and 10.1%, respectively. Frequency characteristics of the co-existence of these genotypes have not been studied yet [9].

## Discussion

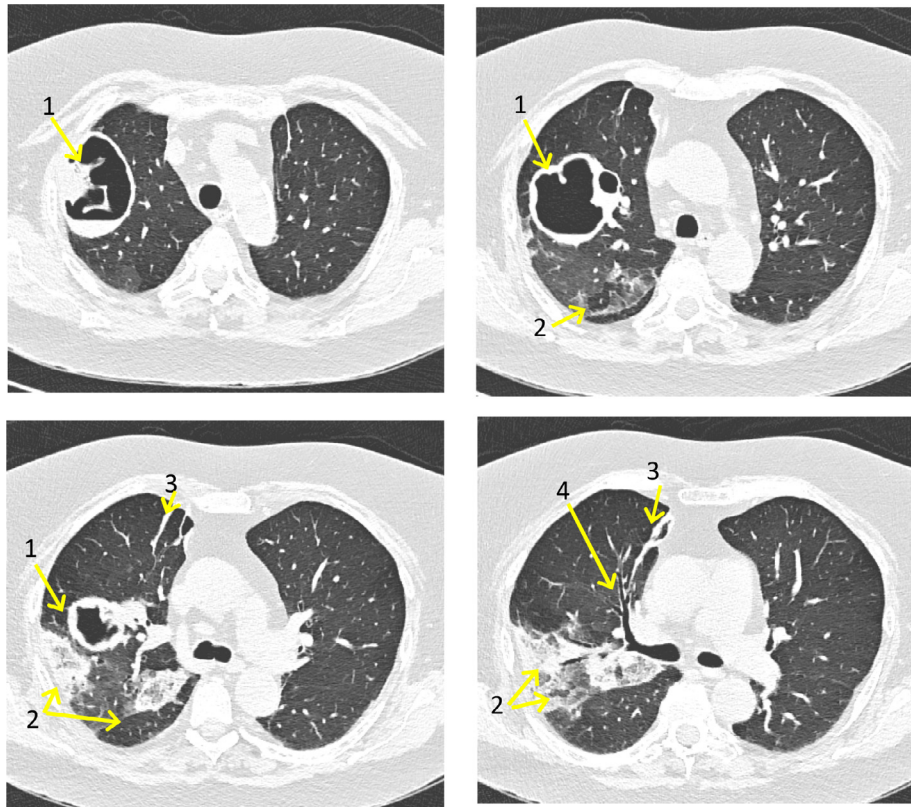
According to published studies, the septicopiemic form of salmonellosis in an immunocompetent patient develops exceptionally rarely. Therefore, to date, the causes of generalization of infection in such cases have not been thoroughly studied. Pulmonary tissue involvement is even less common. Infection can spread into the lungs in various ways: contact, hematogenic, with aspiration of the gastrointestinal tract secretion [10,11].

In the presented clinical case, a generalized form of salmonellosis developed probably due to the presence of Asp299Gly and Thr399Ile polymorphisms in the TLR4 gene, which caused a reduced sensitivity to its specific substrate – LPS of Gram-negative bacteria and elevated the risk of sepsis development [5, 6]. Since the patient had no cases of infection

with gram-negative flora before the presence of pathology of the immune system could only be assumed retrospectively. In addition, on the basis of anamnestic data, we can think about the hereditary nature of these changes, since the mother of the patient years had typhoid fever at her 30s, also caused by a gram-negative pathogen – *Salmonella typhi*. It is worth mentioning that receiving gastroprotectors for a long time was another, since *Salmonella* is sensitive to the action of the acidic environment of the stomach [10, 12].

To assess the incidence of *Salmonella* pneumonia and analyze the characteristics of this disease, a search was made in the Pubmed database for the keywords *Salmonella* AND *Pneumonia* with the constraint of Clinical Case. The study included only cases of infection with non-typhoid strains of *Salmonella*. 8 articles were found that meet the conditions of the search query (Table 1).

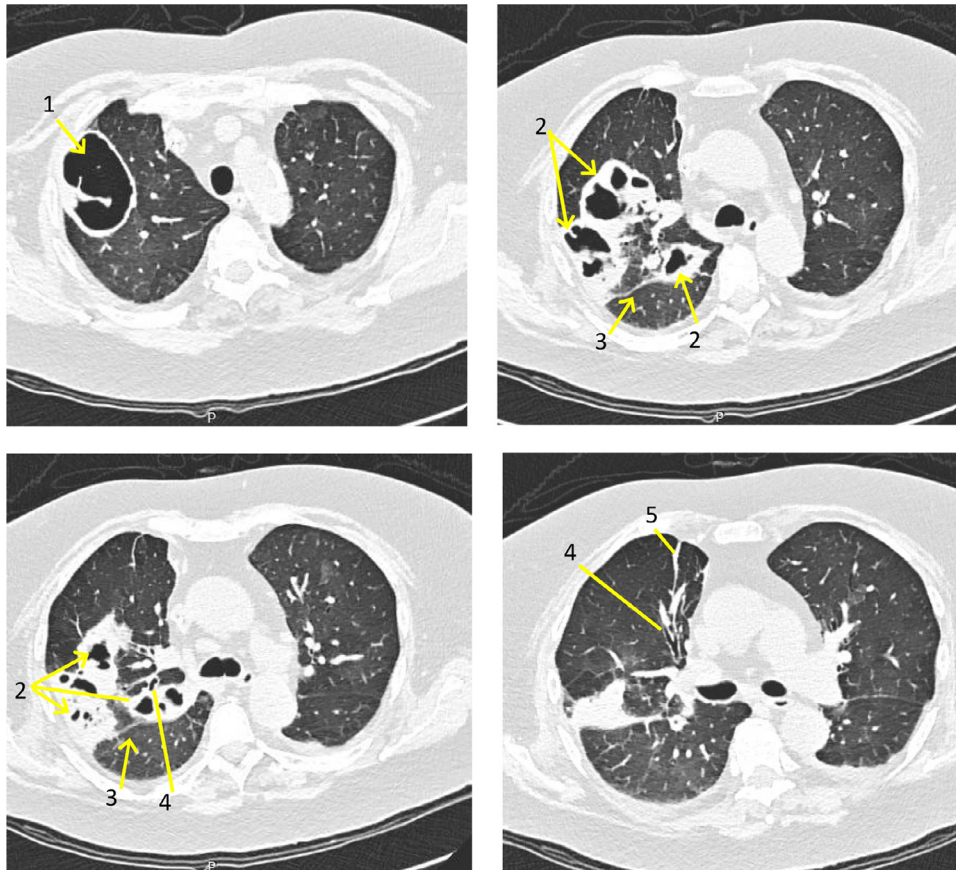
Performed investigation revealed that in patients with generalized salmonellosis (35 patients, 100%), the most common comorbid pathology was immunodeficiency, including oncological diseases (25 patients, 71.4%). The development of the disease in immunocompetent patients was established only in 28.6% of cases (10 patients). This finding shows that the most significant risk factor for the development of *Salmonella* pneumonia is the pathology of the cellular component of the immune system. However, since the



**Fig. 2** – Chest CT at the admission, axial slices. In S1 of the right lung there is a cavity with irregular walls up to 5-mm thick and smooth outer margins and with liquefied content (1). In S1-S2 of the right lung, there are triangular-shaped subsegmental in homogeneous zones of increased attenuation (2). Linear subsegmental atelectasis (3) is visualized in S3 of the right lung. The walls of the segmental bronchi of the right lung are thickened (4).

**Table 1** – Summary table of clinical data of patients with pneumonia associated with non-typhoid Salmonella [10-12,15,16]

Clinical characteristics of patients with pneumonia associated with non-typhoid Salmonella		Number of patients n = 35, 100%
Extrapulmonary manifestations of salmonellosis, n(%)	Gastrointestinal tract	6 (17,0)
	Abscess of the gluteal muscle	2 (5,7)
	sacroiliitis	1 (2,9)
	Sepsis	7 (20,0)
Complication of pneumonia associated with non-typhoid Salmonella, n(%)	Destruction of lung tissue	6 (17,0)
	Pleural empyema	2 (5,7)
Comorbid diseases, n(%)	ARDS	4 (11,4)
	HIV-infected	17 (48,5)
	Lung/pleural neoplasm	3 (8,6)
	Neoplasms of other localizations	5 (14,2)
	Type I diabetes	4 (11,4)
	Pulmonary tuberculosis	1 (2,9)
	Chronic lung disease	1 (2,9)
	Other diseases (schizophrenia, convulsive syndrome, cardiovascular diseases, systemic connective tissue diseases, kidney diseases)	6 (17,0)



**Fig. 3** – Follow-up chest CT on the 7th day of hospitalization. The level of the axial slices corresponds to the slices in **Fig. 2**. There is a decrease in the volume of the cavity (1) in S1 of the right lung and the disappearance of the liquid level in it. The formation of multiple cavities is noted in structure of consolidations in the S1-S2 of the right lung (2). The interlobar pleura is thickened (3). The walls of segmental and sub-segmental bronchi are thickened (4). Subsegmental linear atelectasis in S3 of the right lung remains unchanged (5).

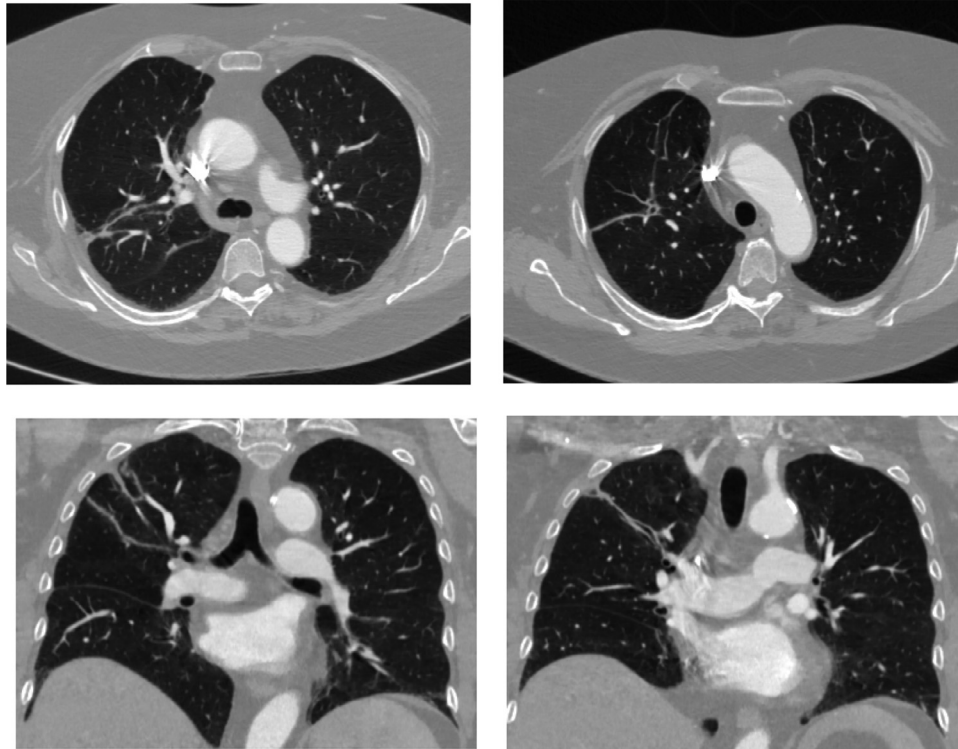
immunologist's consultation and genetic testing was not carried out in any of the presented cases of *Salmonella* pneumonia in immunocompetent patients, it is impossible to categorically assert that they do not have a hidden pathology of the immune system, for example, such as in the presented clinical case.

The diagnosis of "Salmonella sepsis" was established only in 13% of cases (5 patients). The development of pneumonia complicated by an abscess was observed in 4 immunocompromised patients (10.8%). Cases of a combination of extraintestinal salmonellosis and PE, confirmed by angiography, are not presented in the literature.

In the presented clinical case, areas of consolidation of lung tissue with destruction cavities, localized in the territory of the thrombosed branch of the pulmonary artery, were identified during the CT of chest organs and CT angiography. These consolidation zones can be regarded as infarct pneumonia formed after PE, since their triangular shape in S1 and S2 of the right lung and linear subsegmental atelectasis in S3 of the right lung are typical for PE. However, the formation of cavities in the area of aseptic infarction is not typical for PE and occurs only in 4%-7% of cases. Risk factors for destruc-

tive changes in the lung tissue against infarct pneumonia are a large infarct zone (>4 cm), older age, presence of heart failure or chronic lung disease. The probability of cavity formation is increased when infarction zone is infected or PE occurs against an infectious disease, often caused by gram-negative flora [7,13,14]. In the presented clinical case, there was a combination of 2 risk factors for cavitation in PE: multiple massive zones of pulmonary parenchyma infarction (>4 cm) and concomitant *Salmonella* sepsis. The presence of septic thrombophlebitis makes impossible exclusion of septic PE. An embolism with infected thrombi is an additional risk factor for abscess formation in the infarction zone, which is observed in 44% of these patients [15].

It is worth noting that *Salmonella*, when they reach a concentration of >10/mL of blood serum, can induce thrombosis by platelet activation in various ways and probably inactivating the anticoagulant system [13]. Mechanisms of immunothrombosis have not been understood well yet. To our knowledge, there is a single article in the literature describing salmonellosis complicated by deep vein thrombosis of the left lower limb and PE. But no angiographic evidence of thromboembolism was shown [16].



**Fig. 4 – Chest CT 3 months after discharge. In the S1 of the right lung there are fibrous cords replaced the cavities.**

## Conclusion

The presented clinical case illustrates the rare course of nontyphoid generalized salmonellosis with the development of destructive pneumonia and PE. It demonstrates the need for a multidisciplinary approach in the treatment of patients with severe and atypical forms of infectious diseases.

Literature data analysis revealed that such a course of the disease is characteristic to a greater extent of immunocompromised patients. The presence of a cellular immunity pathology determined easier gastrointestinal invasion of *Salmonella* and, consequently, the tendency to generalization. In our case, extraintestinal salmonellosis was triggered by a latent defect in the Th1-mediated immunity system. The violation of local protection factors played an additional covert role in the generalization of the disease. Also, an accurate analysis of observed clinical cases demonstrated the importance of monitoring coagulation activity to timely diagnosis of thrombosis development because of prothrombotic activity of *Salmonella*.

## Authors' contributions

**Anastasia D. Strutynskaya** - development of the concept and design of the article, writing text, responsibility for the integrity of all parts of the article. **Maria A. Karnaushkina** - development of the concept and design of the article, writing the text, editing. **Igor E. Tyurin** - writing the text, approval of the

final version of the article, editing. **Irina S. Komarova** - collection and processing of material.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.radcr.2020.05.076](https://doi.org/10.1016/j.radcr.2020.05.076).

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