

CASE REPORT

Serious imported infections: A focus on *Chromobacterium violaceum*

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ABSTRACT

The authors report on the main threats in the Czech Republic connected with travel and migration. The spectrum of diseases differs in the group of Czech citizens departing abroad, especially in the tropics and subtropics, from infections detected in foreigners, in particular from developing countries.

A case report of sepsis caused by the exotic bacteria *Chromobacterium violaceum* is added to illustrate the potential severity of imported infection. A 54-year-old man acquired the infection during a diving holiday in Thailand. The disease began as a local ear infection, and progressed to septic shock with multiple organ failure and ischemic necrosis of all extremities. The original infection was cured but the patient eventually died due to subsequent complications. In order to properly diagnose and treat such rare diseases, we feel useful to study their pathogenesis (Tab. 2, Ref. 16). Text in PDF www.elis.sk.

KEY WORDS: imported infections, *Chromobacterium violaceum*, sepsis.

Introduction

Imported infections can be defined as infections acquired in a foreign country. When imported infections are understood in this way, then majority of diseases are common ubiquitous diseases such as pneumonia, sinusitis, urinary tract infections and acute infectious diarrhea. Focusing on diseases that are subject to reporting, salmonellosis and campylobacteriosis are the most common imported diseases (1); this result is due to careful investigation and reporting of etiology of diarrheal diseases, which has been practiced in the Czech Republic for a long time.

Most statistics show that the number of imported infections cases is increasing. This is probably due to the easy travel that becomes available to more and more people, as well as shortening of time needed to overcome long distances. It is possible to move thousands of kilometers within a few hours or one day; this time is much less than the incubation period of the vast majority of infectious diseases.

This issue deals with imported infections in the narrow sense of the word, i.e. those that do not occur naturally in the home country and have been introduced here as a result of the migration. These diseases can represent a serious health problem for several reasons:

- As they do not occur naturally in the home country, neither the affected person nor the first-contact physicians are ready for this option; the physicians do not count on this possi-

bility in differential diagnosis, and even if they do, they usually do not make the right examinations to confirm the diagnosis.

- There is usually little awareness of the appropriate isolation, so that the affected individuals remain in contact with other unprotected population or, conversely, are subjected to unnecessarily stringent isolation.

From a practical point of view, it is appropriate to distinguish two basic types of imported infections: (a) infections that have affected the home country's citizens after returning from abroad; (b) infections found in aliens. Both these groups will be discussed in terms of the Czech Republic.

Imported infections in the Czech citizens traveling to European countries

According to available information, Czech citizens leave for longer stays abroad (more than 1 week) mainly to three destinations (2):

- Slovak Republic, the most common reason is to visit relatives; trips to Slovakia are common throughout the year;
- Alpine countries, especially Austria, where skiing and winter tourism are the most frequent reasons for the trip;
- Mediterranean countries that are the most favorite tourist destinations during the summer holidays; this includes in particular Croatia, Italy, Greece and Spain.

The last group is the most important in terms of infectious disease risk. Citizens in coastal resorts with lower sanitation levels are at risk of various foodborne infections (campylobacteriosis, salmonellosis, shigellosis, hepatitis A, etc.). In addition to these common diseases, some mosquito-borne (leishmaniasis, West Nile fever) or tick-borne infections (Marseille fever) can be acquired.

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Imported infections in the Czech citizens traveling to tropical and subtropical regions

The available data show that about half of the travelers use the travel agency services; others arrange their journey individually (2). The following infectious diseases are the most important for these travelers:

- Febrile infections transmitted by mosquito or other blood-sucking insect (malaria, visceral leishmaniasis, dengue, chikungunya, West Nile fever, Zika virus infection, yellow fever, Japanese B encephalitis and others). The risk of transmission of these infections depends on local conditions, such as season, air temperature and humidity, wind, etc., which determine the frequency and activity of insect vectors. Some of these diseases can be prevented by early vaccination or chemoprophylaxis.
- Foodborne infections (typhoid fever, cholera, amoebiasis, giardiasis, various intestinal helminthiasis, viral hepatitis A and E). The risk depends on the way of eating and the quality of drinking water.
- Sexually transmitted infections and blood-borne infections (HIV infection, hepatitis B and C, syphilis, gonorrhea, chlamydia genital infections, lymphogranuloma venereum and others). The risk of these imported infections is related to the popularity of sex tourism and the use of indigenous healing and beauty practices (tattoos).
- Various skin infections due to agents uncommon in Europe (cutaneous leishmaniasis, larva migrans cutanea, myiasis, tungosis; cutaneous diphtheria or anthrax, etc.). The risk depends on the specific activities of travelers. With the initial skin infection starts also a rare disease caused by the bacterium *Chromobacterium violaceum*; a case report of such disease is described in the following text.
- Severe pneumonia caused by inhalation of unusual pathogens (hantavirus infections, legionellosis, exotic fungal infections like histoplasmosis, coccidioidomycosis, blastomycosis, sporotrichosis, and others). These diseases are rare but very dangerous. They are difficult to diagnose and often difficult to treat, and their lethality is relatively high.
- Viral hemorrhagic fevers (Lassa, Ebola, Marburg and others) and potentially lethal coronavirus infections (MERS, SARS) represent a separate issue. They cause severe systemic infections with high lethality and can be transmitted from person to person not only by contact but also by air. Also, no reliable causative treatment or vaccine is available so far. Thus, such diseases are referred to as highly dangerous infections. To be prepared for their introduction into its territory, each developed country established a rapid diagnostics system and one or more special isolation units equipped with air-condition connected to the highly efficient anti-viral filters, full-body protective clothing (suit) for medical personnel, solid waste decontamination facilities and sewage treatment plants. In the Czech Republic, such a unit was established at the Department of Infectious Diseases in the Na Bulovce Hospital in Prague. A similar unit was built at the Department of Infectology and Geographical Medicine in Bratislava.

Tab. 1. The most important infections imported from tropics and subtropics and their specific risk.

Examples of serious infections in which wrong/late diagnosis (i.e. delay of causative treatment) significantly worsen the patient's prognosis	Examples of serious infections in which wrong/late diagnosis (i.e. delay of the isolation precautions) means epidemiological risk to the entire population
malaria	tuberculosis
typhoid fever	typhoid fever
diphtheria	diphtheria
brucellosis	cholera
plague	shigellosis
visceral leishmaniasis	pandemic influenza, avian influenza
amoebic liver abscess	severe coronavirus infections (MERS, SARS)
<i>Chromobacterium</i> infection	Ebola, Lassa fever

MERS = Middle-East respiratory syndrome, SARS = severe acute respiratory syndrome

Tab. 2. Infections imported to the Czech Republic in 2001–2017 (1).

Disease	Number of reported cases
campylobacteriosis	3801
salmonellosis	3703
animal bite or injury ¹	1337
shigellosis	1054
giardiasis	667
viral hepatitis A	601
scabies	601
trichuriasis	537
ascariasis	500
dengue fever	446
viral gastroenteritis	362
malaria	255
viral hepatitis B	254

¹Persons who are vaccinated against rabies used to be referred in category “animal bite or injury”. The vast majority of animal injuries are completely banal events that would heal without medical assistance. However, if there is even a very little risk of rabies transmission, these persons are vaccinated and so they appear in the statistics.

Table 1 lists the most important imported infections that every physician who provides care to returnees from abroad (including physicians of the emergency departments of large hospitals) should know. Table 2 shows the number of the most important reported infections imported to the Czech Republic in the period 2009–2018.

Imported infections in foreign visitors to the Czech Republic

There is a somewhat different spectrum of diseases among foreign visitors who come to the Czech Republic for both short-term and long-term stays. For the purpose of short-term tourism or business trips, our closest neighbors – Slovaks, Germans and Poles – come to the Czech Republic. Especially Americans, Russians and East Asians, i.e. Chinese, Koreans and Japanese, come as tourists from more distant countries. The main destination of these tourists is Prague and, to a lesser extent, Karlovy Vary and other West Bohemian spas (2). Imported infections are rarely diagnosed in these groups of visitors.

Foreigners who come to the Czech Republic for a long-term stay or live here permanently represent considerably higher risk. The number of these foreigners reached 547,000 as of 31/12/2018, which is 4.8% of the total population. For comparison, the share

of foreigners in Slovakia is only 1.3% and in Austria 15.2% (3). The most frequently registered nationalities in the Czech Republic other than Slovaks are Ukrainians, Russians and Vietnamese. The risks of imported infectious diseases in these three ethnicities differ somewhat. On the whole, in citizens of these nationalities it is necessary to take into account infections, which were largely eliminated in the Czech and Slovak Republic thanks to the continuous vaccination, i.e. tuberculosis or measles. Also, higher incidence of HIV and other sexually transmitted diseases is referred in the Ukrainian and Russian populations whereas an increased risk of various parasitic infections, viral hepatitis B, and tuberculosis (including extrapulmonary forms) is found in people from tropical and subtropical countries (3,4).

The number of migrants coming from Africa or the Middle East is relatively low in the Czech Republic; these migrants mostly passed the initial health check and their health status was good. According to statistics, the number of illegal migrants in the Czech Republic is around 5,000 (2).

***Chromobacterium violaceum* infection (CVI)**

This rare but potentially fatal disease occurs especially in the East Western Pacific, the Southeast USA and South-East Asia (5). In Europe, the infection has not been reported yet except for a case from Italy which manifested with cervical lymphadenitis in a 14-year-old Italian resident born in Guinea (6). Thus, *C. violaceum* seemed to pose no threat to Europeans.

The pathogenesis of CVI has not been fully understood. In the autopsy of an animal model, there were multiple small nodules in tissues consisting of bacteria surrounded with degenerate neutrophils and fibrin exudate, along with multifocal thrombosis and local hemorrhage. Numerous bacteria were also found inside blood vessels (7). Such a microscopy supports the findings that *C. violaceum* is relatively resistant to phagocytosis (8).

The course of disease depends on the portal of entry of the infection. If the disease starts as a skin and soft tissue infection that occurred after a minor injury, it develops relatively slowly within a few days before the patient's condition begins to deteriorate rapidly. In the meantime, the traveler infected in an endemic region can return to his home country (9,10). Faster and usually fatal course was reported when bacteria had been inhaled (11, 12). A plausible explanation is that bacteria grow relatively slowly in the connective tissue. Once they penetrate into the bloodstream, they quickly disseminate to distant tissues, especially those containing many lymphocytes and macrophages (liver, spleen, and lungs). The dissemination is associated with a rapid deterioration and development of sepsis and multiple metastatic abscesses.

Two conclusions can be drawn from this description: (a) Affinity of *C. violaceum* to specific organs could be explained by its ability to survive in macrophages that transport the phagocytized bacteria into lymphoid tissues. This hypothesis of intracellular surviving correlates well with the recommendation for long-term antibiotic treatment because of a risk of relapse following a standard length of therapy (13). (b) Also, *C. violaceum* is able to survive and multiply in the bloodstream what is unusual. For most bacteria, cir-

culating blood is a very hostile environment, even in the absence of specific antibodies. Thus, *C. violaceum* seems to be relatively resistant to complement and other natural bactericidal substances in blood. Pathogenicity of *C. violaceum* is similar to *Yersinia pestis* or *Bacillus anthracis*.

Published cases of CVI were mostly severe, with an average mortality of about 50%. Mortality of disseminated infection was even higher, around 60–80% (5, 13,14). However, this proportion is contradicted by two independent, detailed studies recently carried out in Northern Australia which showed substantially lower mortality of <10% (15,16). The Australian authors tried to explain the discrepancies by two credible hypotheses: (a) A reporting bias because severe cases are more attractive for publication. (b) A variable expression of virulence factors of *C. violaceum* in different geographical locations. We submit another hypothesis: Local people, especially agricultural workers, are occasionally exposed and/or colonized by *C. violaceum* and can be protected by specific antibodies. It would also explain why children, young people and other “naive” individuals like travelers were particularly affected by the disease.

Case description

A 54-year-old man had spent a 3-week sea diving holiday in Thailand. At the end of holiday, he complained of an earache and auricle swelling. After arrival home, a right-sided tympanic membrane rupture was diagnosed; a swab for culture was sampled and the patient was given oral clindamycin. Because of fever up to 40 °C, he was admitted to a regional hospital, with leukocytes 22.6 x10⁹/L and C-reactive protein 332 mg/L. The ear swab yielded *Chromobacterium violaceum*. Despite three-day treatment with gentamicin 240 mg/d the patient remained febrile, with mild diarrhea and vomiting, and was transferred to our department.

On admission he complained of dyspnea and right upper abdominal pain. Heart rate was 114 b/min, blood pressure 106/72 mmHg, respiratory rate 28/min, and oxygen saturation 93%. Ultrasonography showed a mild splenomegaly. Meropenem 3 g/d was started. Twenty hours later the patient suffered from cardio-respiratory arrest, was resuscitated and put on mechanical ventilation. *C. violaceum* was isolated from a blood culture, sensitive to fluoroquinolones, aminoglycosides, and carbapenems, but resistant to aminopenicillins, cephalosporins, and colistin. Treatment was increased to meropenem 6 g/d and ciprofloxacin 800 mg/d. A multiple organ failure developed. The first CT on day 5 showed multiple liver abscesses (5–10 mm). The follow-up CT on day 24 showed regression of small abscesses but a new big liver abscess (33 x 38 x 56 mm) and three other intra-abdominal abscesses. All were drained under CT navigation. In the following weeks, new intra-abdominal abscesses occurred but repeated CT navigated punctures and drainages were too little avail. On day 44 an open laparotomy with necrectomy and drainage was performed, followed by seven more surgical inspections.

As a consequence of the initial septic shock and disseminated intravascular coagulopathy, all four of the patient's extremities suffered from ischemic necrosis. Three weeks after admission

all extremities had to be amputated at the level of forearms and below the knees.

The patient remained febrile with high CRP and leukocytes despite multiple adjustments to the antibiotic therapy. These were due to persistent sepsis with recurrent abdominal abscesses as well as secondary respiratory and urinary tract infections caused by nosocomial pathogens. After 170 days of treatment, the fever gradually disappeared; CRP and leukocytes decreased and antibiotic therapy was finished. On day 200 the patient was transferred to a long-term intensive care facility. Two months later he died of pneumonia.

We conclude that our patient acquired the infection in endemic area during typical activities. External otitis was thought to be the portal of entry. Another case of lethal sepsis originating in ear has been described by Jitmuang(15). Initially the infection progressed slowly with local symptoms, and the patient could return home. A septic shock developed after he had been admitted to our department, i.e. eight days after the onset of symptoms. It caused not only a multiple organ failure but also severe ischemia of the peripheral parts of the limbs which resulted in amputation.

Conclusion

The risk of import of rare infections is increasing because of opportunities for easy and fast travel to remote countries. If a traveler is infected with *Chromobacterium violaceum* via a skin injury what is the most common portal of entry, he can still return to his home country before developing sepsis. It is therefore important to count with such an infection also in the mild climate regions. The disease should be considered in patients with rapidly evolving sepsis and multi-organ abscesses, and a history of outdoor water activities in endemic areas. Rapid diagnosis and appropriate antimicrobial therapy can be life-saving. A combination of carbapenem and fluoroquinolone can be recommended as the most reliable therapy.

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