



Tick-borne lymphadenopathy acquired in Serbia – report of two cases

Ubodom krpelja uzrokovana limfadenopatija – prikaz dve bolesnice zaražene u Srbiji

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Abstract

Introduction. Acronym tick-borne lymphadenopathy (TIBOLA) (*Derma-centor*-borne necrosis erythema and lymphadenopathy – DEBONEL, scalp eschar associated with neck lymphadenopathy – SENLAT) comprises clinical diagnosis of tick-borne symptoms of cervical or occipital lymphadenopathy with inoculation eschar at the site of tick bite on scalp. Since the first description, it was proved to be associated with several infectious agents, most frequently *Rickettsia slovaca*, or less often other spotted fever group *Rickettsiae* (*Rickettsia raoulti* and *Rickettsia rioja*), and gained an emerging infectious disease status in Europe. *Derma-centor* ticks serve as vectors and possible natural reservoir. The course is in most cases benign and infection is limited. Doxycycline is the recommended initial treatment, both for adult and most cases in children. **Case report.** Two subjects who acquired the disease caused by tick bites in Vojvodina region of Serbia are presented. Both patients are females. A tick was removed from the scalp, and several days later doxycycline treatment started because of the inflammatory symptoms of lymph node enlargement. Diagnostic eschar appeared in both patients during doxycycline treatment. After a switch to ciprofloxacin, inflammatory symptoms subsided, but the complete healing of scalp necrosis took longer than one month, with residual cicatricial alopecia. **Conclusion.** Although rare, it is necessary to include TIBOLA in a spectrum of epidemiologic risks in cases of tick bites.

Key words:

tick borne diseases; derma-centor; rickettsia; diagnosis; treatment outcome; serbia.

Apstrakt

Uvod. Akronim *tick-borne lymphadenopathy* (TIBOLA) (*derma-centor* borne necrosis erythema and lymphadenopathy – DEBONEL, scalp eschar associated with neck lymphadenopathy – SENLAT) podrazumeva kliničku dijagnozu simptoma vratne limfadenopatije i inokulacione eshare na koži poglavine uzrokovanih ubodom krpelja. Od prvih opisa dokazana je uzročna uloga nekoliko infektivnih agenasa, najčešće *Rickettsia slovaca*, ređe drugih rikecija *spotted fever grupe* (*Rickettsia raoulti* i *Rickettsia rioja*). U Evropi je stekla status infekcije u nastajanju. *Derma-centor* krpelji su vektori i verovatni prirodni rezervoar ove grupe rikecija. Tok je obično nekomplikovan i infekcija je ograničena. Doksiciklin je preporučena terapija za odrasle i pedijatrijske bolesnike. **Prikaz bolesnika.** U radu su prikazana dva slučaja TIBOLA stečene ubodom krpelja u Vojvodini i Srbiji. Ubod krpelja kod obe bolesnice bio je u predelu poglavine. Krpelj je uklonjen od strane lekara. Kod obe bolesnice je nakon par dana započeta terapija doksiciklinom zbog uvećanja limfnih čvorova vrata i potiljačne regije. Dijagnostička eshara pojavila se kod obe bolesnice tokom terapije doksiciklinom. Nakon uvođenja ciprofloksacina u terapiju upalni simptomi su se povukli, ali za potpuno zaceljivanje nekroze kože poglavine bilo je potrebno više od mesec dana, sa rezidualnom ožiljnom alopecijom. **Zaključak.** Mada je TIBOLA retka infekcija, mora se prepoznati kao epidemiološki rizik u slučaju uboda krpelja.

Ključne reči:

bolesti, ubodom krpelja izazvane; derma-centor; rickettsia; dijagnoza; lečenje, ishod; srbija.

Introduction

Since initial descriptions of cases with scalp necrosis and lymphadenopathy after tick bite as a clinical syndrome caused by *Rickettsia slovaca* in 1997, the disease gained an emerging

infectious disease status in Europe, and reports were observed worldwide^{1,2}. Terminology of this clinical syndrome is still not unified; most cases are referred to as tick borne lymphadenopathy (TIBOLA), *derma-centor*-borne necrosis erythema and lymphadenopathy (DEBONEL), or scalp eschar associated with

neck lymphadenopathy after a tick bite (SENLAT). Clinical picture characteristics are: several days after a tick bite enlargement of retroauricular or cervical lymph nodes on the scalp occurs, with skin inflammation and formation of scalp necrosis (inoculation eschar) at the spot of the tick bite. In most cases, the course is benign and infection is limited.

Two patients infected by tick bites in Vojvodina region are presented, being the first cases of this clinical entity recorded in Serbia.

Case report

Case one

A fifty-eight-years-old female patient, with unremarkable previous medical history had tick bite in October 2014, in Bačka Palanka region. A tick attached on the scalp (left crown region) was noticed the next day while combing, and removed in primary care. A week later, the patient experienced left-sided headache, and the following day, she noticed enlarged lymph node at the left mandible angle. Doxycycline 200 mg *per os* daily started on the day 10 after the bite, but without improvement neither in pain nor lymph node enlargement and on the day 12, the patient noted a crust at the site of the tick bite. On the day 14, during dermatological examination, the patient presented with 2 cm scalp eschar, palpable cervical lymph node near left mandible angle (Figure 1). Due to presumed lack of response to doxycycline, ciprofloxacin 1g *per os* daily was added with topical antiseptic gel (octenidine hydrochloride), and a headache subsided in 3 days. Dual antibiotic treatment continued, doxycycline from 10th–30th day from the tick bite and ciprofloxacin from 14th–24th day. The demarcated scalp eschar was removed on the day 30 after the bite as well as residual erosion covered with hydrocolloid dressing, but on the day 38 eschar of smaller size reappeared. The patient did not appear for further follow-up and no data were available about the time needed for the complete healing of a skin lesion and size of residual alopecia.



Fig. 1 – Scalp eschar of patient 1.

Case two

A forty-five-year-old female patient, with unremarkable previous medical history. A tick bite in May 2016 in Vrbas region had a tick was removed from the central-frontal scalp region one day later. On the day 2, the patient noticed enlargement of left retroauricular lymph node and started treatment with doxycycline 200 mg *per os* daily (Figure 2). On the day 9 after a tick bite, swelling of forehead appeared, which spread to lower eyelids on the day 10, and due to suspect doxycycline angioedema, the patient was referred to a dermatologist. On the day 10, the spot of a tick bite was inflamed and oozing (Figure 3); doxycycline was discontinued because of presumed inefficacy, and a combination of amoxicillin 2 g and ciprofloxacin 1g *per os* daily continued to be taken for the following 2 weeks. Inoculation eschar was evident 13 days after the bite, determining clinical diagnosis of TIBOLA (Figure 4). Demarcation of eschar was slow during the following month, with residual atrophic alopecia 1 cm in diameter.



Fig. 2 – Enlarged retroauricular lymph node of patient 2.



Fig. 3 – Tick bite spot inflammation, 3 days before the eschar in patient 2.



Fig. 4 – Eschar during demarcation phase in patient 2.

In both patients basic laboratory analyses (erythrocyte sedimentation rate – ESR, blood cell count, C reactive protein, fibrinogen level, liver enzymes) were normal, aerobic and anaerobe bacteriological cultures of eschar swab were negative, and *Borrelia burgdorferi* ELISA serology, as well. Serological analyses for *Rickettsia* species (ELISA and Weil Felix test), cultivation of *Rickettsia* and molecular detection of *Rickettsial* DNA were not available. Both patients did not approve skin biopsy and could not report any activity in nature that had preceded tick bite.

Discussion

Acronym TIBOLA (DEBONEL, SENLAT) comprises clinical diagnosis of tick-borne symptoms of cervical or occipital lymphadenopathy with inoculation eschar at the site of a tick bite on the scalp. During 2 decades since the first description, it proved to be associated with several infectious agents, most frequently *Rickettsia slovaca*, or less often other spotted fever group *Rickettsiae* (*Rickettsia raoulti* and *Rickettsia rioja*)³. Other bacteria were rarely involved (*Francisella tularensis*, *Bartonella henselae*, *Coxiella burnetii*)^{4,5}. *Dermacentor* ticks (*Dermacentor marginatus* and *Dermacentor reticulatus*) are vectors specific for the transmission of infectious agents of TIBOLA which are also a possible natural reservoir host for *Rickettsia slovaca*. *Dermacentor* ticks differ from *Ixodes* species in larger unfed adult body size (> 5 mm vs. 2–4 mm of *Ixodes*), better tolerance to dry and cold environment, longer activity period du-

ring colder months, longer feeding time (*Dermacentor* spend attached couple of days vs. 7–9 hours of *Ixodes*) and natural habitat (*Dermacentor* is more frequent in steppe meadows, while *Ixodes* prefer more humid environment in higher vegetation, forests and bush). *Dermacentor* ticks frequently carry *Rickettsia* species of spotted fever group, sometimes multiple *Rickettsia* strains, or *Coxiella burnetii*, *Francisella tularensis*, and are not optimal vectors for *Borrelia burgdorferi* transmission⁶.

Typical TIBOLA patients are women and children with *Dermacentor* tick bite on the scalp, what is hypothesized to be a consequence of parasitizing habit of adult *Dermacentor* ticks, for hiding in a shelter of long hair-bearing areas (tail and mane) while feeding on animal hosts. Recent study from Hungary demonstrated that a contact with horses is independent risk factor for TIBOLA infection. Possible differences between contact with horses and other large domestic animals were not specified (no patient marked contact with cattle, goats, sheep)⁷. Although outnumbered in nature by *Ixodes* species, spatial distribution of *Dermacentor* ticks has been increasing in recent decades, together with more frequent human and animal infection with *Dermacentor*-specific pathogens^{8,9}.

Diagnostic hallmarks of TIBOLA are inoculation eschar on scalp and cervical lymphadenopathy, sufficient for the clinical diagnosis. For the precise identification of infectious agent serological tests (ELISA) are frequently not sensitive enough, due to low titer in localized infection and cross reactivity within spotted fever group *Rickettsia*. Weil-Felix agglutination test with OX19 and OX2 antigens, as non expensive and widely used screening diagnostic for scrub typhus in the Middle and Far East countries, can be expected to be positive for TIBOLA, but with even lower sensitivity and specificity¹⁰. Cultivation of *Rickettsia* is difficult and not routinely done in most microbiological laboratories.

Molecular diagnosis (polymerase chain reaction – PCR) is the most specific method, and can be performed on patient samples (serum, skin biopsy, eschar swab, lymph node aspirate) or tick tissue^{11,12}. The course of the disease is usually benign. Incubation period from the tick bite to the appearance of first symptoms is 4–7 days. In the acute phase, apart from inoculation eschar and lymphadenopathy, patients can experience headache, mild infection signs (malaise, moderate fever) or localized inflammatory symptoms (facial oedema, pain of skin or lymph nodes).

It is of diagnostic importance that there is a lack of clinical signs of other Rickettsial diseases, i.e., Mediterranean spotted fever [eschars on other extracranial body sites, multiple eschars, maculopapular centrifugal exanthema (hands and feet), purpura, high fever]. Healing of eschar takes one to two months, and in up to one third of the patients residual cicatricial alopecia is permanent.

In both patients in this report, clinical symptoms were developing during the doxycycline therapy, which is recommended as the first line treatment for TIBOLA, and other *Rickettsioses*. The role of antibiotics in TIBOLA were previously investigated and it can be concluded that early treatment with doxycycline or azithromycin can shorten the course of the disease¹³. Although the infective cause in both cases in this report could not have been precisely characteri-

zed, it can be hypothesized that presumed inefficacy of doxycycline on the appearance of eschar is the consequence of Rickettsial tropism for endothelial cells, causing localized increase of inflammatory and procoagulant factors mediating tissue injury.

Also, the question of post-exposure antibiotic prophylaxis in TIBOLA has not been concluded in literature, but our cases suggest that if not administered immediately after tick bite, doxycycline cannot prevent eschar appearance.

Presented cases are the first ones described as acquired at the territory of Serbia. It is likely that the TIBOLA (DEBONEL, SENLAT) in Serbia is more unrecognized and underreported than absent, because in neighboring countries disease is not considered to be rare. In Hungary, a country of origin of first TIBOLA cases, patient data are followed in registry of medical institution specialized for the treatment and surveillance of tick borne diseases.

This approach enables more active and precise actions, especially in the light of that since the description of *Borrelia*

burgdorferi in 1982 as the causal agent of Lyme disease, eleven more tick-transmissible pathogens were defined in Europe¹⁴. Recent study from Bosnia and Herzegovina revealed range of 6%–66% positivity to *Dermacentor* ticks (*marginatus* and *reticularis*) for *Rickettsia slovacica* and *Rickettsia raoulti*¹⁵.

Conclusion

Although TIBOLA is rare infection, it is necessary to include it in a spectrum of epidemiologic risks in case of tick bite in Serbia. It is of public importance in Serbia to educate patients for self-help in case tick bite occurs (not to postpone tick removal until visiting a physician for a proper mechanical tick removal technique without the use of chemicals), with special emphasis on preventive measures for frequent skin and scalp check-ups during outdoor activities in regions with abundant tick population.

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