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CLINICAL REASONING: CASE REPORT

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Human granulocytic anaplasmosis acquired in Switzerland: a case report

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Summary

BACKGROUND: Human granulocytic anaplasmosis, caused by Anaplasma phagocytophilum, *is a tick-borne disease endemic* in North America that is emerging in Europe and may be underdiagnosed in Switzerland.

CASE PRESENTATION: A man in his early seventies receiving methotrexate for ankylosing spondylitis and exposed to ticks presented with a 2-day history of fever, headache and dizziness. Despite empirical broad-spectrum beta-lactam and macrolide therapy, high fever of undetermined origin persisted, and neurological deterioration occurred (somnolence, dysarthria, ataxia, diplopia). Cerebrospinal fluid analysis showed 10 mononuclear cells/µL (normal <5 cells/µL) and protein 476 mg/l (150–450 mg/l). Brain MRI revealed nonspecific leukoencephalopathy. Intravenous doxycycline 100 mg twice daily was empirically initiated on day 7 after symptom onset, resulting in clinical cure within 3 days. Human granulocytic anaplasmosis was retrospectively confirmed by IgG seroconversion against *A. phagocytophilum* after 6 weeks (8-fold titre increase from <1:64 to 1:512).

DISCUSSION: Human granulocytic anaplasmosis represents a diagnostic challenge in non-endemic areas. The human granulocytic anaplasmosis clinical spectrum ranges from mild self-limiting flu-like illness to severe, life-threatening multisystem disease, especially in older immunocompromised patients. Acute-phase diagnosis relies on blood PCR testing. Seroconversion with a 4-fold increase in IgG titre within 2–4 weeks is the gold standard for diagnosis in the convalescent phase. Doxycycline is the first-line antimicrobial therapy.

CONCLUSION: Human granulocytic anaplasmosis is an emerging tick-borne disease which can be acquired in Switzerland. Early diagnostic work-up using blood PCR and empirical doxycycline therapy are key in patients at risk of exposure to ticks who present with severe acute febrile illness without an alternative diagnosis.

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Introduction

Anaplasma phagocytophilum is a tick-borne intracellular bacterium transmitted by *Ixodes* ticks. Human granulocytic anaplasmosis is endemic in North America. As a significant public health concern, human granulocytic anaplasmosis is a notifiable disease; in the US, cases are reported to the Centers for Disease Control and Prevention (CDC) [1] . Mortality rates of 4% and 18% have been reported in North America in immunocompetent and immunocompromised patients, respectively [2].

Symptoms usually occur one to two weeks after exposure to an infected tick [1-3]. Most infections are asymptomatic or cause a mild self-limiting flu-like illness, whereas a minority progress to severe multisystem disease with leucopenia, thrombocytopenia, hepatitis, renal failure or encephalopathy [2, 3].

The first European human granulocytic anaplasmosis case was reported in Slovenia in 1997, followed by cases from other European countries, including those bordering Switzerland: Austria, France (Alsace) and Germany [3]. In Europe, *A. phagocytophilum* is transmitted by the tick *Ixodes ricinus,* the vector of *Borrelia burgdorferi* sensu lato, tick-borne encephalitis virus, *Francisella tularensis*, *Rickettsia* spp., Ehrlichia spp. and Neoehrlichia mikurensis [3, 4].

In Switzerland, *A. phagocytophilum* has been detected in *Ixodes ricinus* ticks [5], while a unique locally acquired human case was reported in 2022 [6]. We report a serologically documented human case of acute human granulocytic anaplasmosis acquired in Switzerland.

Case presentation

A man in his early seventies, receiving weekly methotrexate for ankylosing spondylitis and apixaban for atrial fibrillation, came to the emergency department with a 2-day history of high-grade fever with chills, generalised weakness, headache and dizziness. He presented in summer, i.e. during the peak tick activity season in Switzerland. He did not recall a recent tick bite, but reported daily outdoor activities in a rural area, particularly gardening, with likely exposure to ticks. He reported no recent travel or close contact with sick individuals or animals.

On admission, his temperature was 39.9 °C, while other vital signs were normal. Neurological examination revealed psychomotor slowing, with mild nonspecific gait instability, without focal neurological deficits or signs of meningism. The remainder of the physical examination was unremarkable.

Laboratory investigations showed leucocytosis, with 14.4 g/l leucocytes (normal 4–11 g/l), including 10.3 g/l neutrophils (1.5–7 g/l) and 2.1 g/l lymphocytes (1–4.8 g/l). Haemoglobin and platelet counts were within the normal range. C-reactive protein was mildly elevated at 22 mg/l (<10 mg/l). Blood coagulation tests, electrolytes, kidney and liver function were normal.

Despite the absence of urinary symptoms, urinalysis showed leucocyturia, proteinuria and bacteriuria. After blood and urine cultures had been collected, empirical ceftriaxone was initiated at admission for suspected urinary tract infection, as no other infectious focus was apparent in this highly febrile, older immunocompromised patient.

The patient remained highly febrile with recurrent chills. Antibacterial therapy was empirically escalated to piperacillin/tazobactam at 2 days and then to meropenem at 3 days because of a persistent septic clinical picture of undetermined origin. After a new dry cough appeared, clarithromycin was added to cover atypical respiratory pathogens.

CT of the neck, chest, abdomen and pelvis revealed no infectious focus. Despite broad-spectrum antibacterial therapy, high fever persisted and the patient's condition deteriorated over the following 2 days, with worsening headache, somnolence, dysarthria, gait ataxia and fluctuating diplopia. Follow-up laboratory tests revealed a normal total leucocyte count, with 1.1 g/l lymphocytes (1–4.8 g/l), normal haemoglobin and platelets. C-reactive protein (CRP) was 8.3 mg/l (<10 mg/l) and procalcitonin (PCT) 0.14 µg/l (<0.05 µg/l). Renal and hepatic function remained normal.

A cerebral angio-CT scan was unremarkable. Apixaban was discontinued in preparation for lumbar puncture.

The discrepancy between persistent high-grade fever and low CRP/PCT levels raised suspicion of an atypical intracellular or tick-borne bacterial infection. Intravenous doxycycline 100 mg twice daily was empirically started 5 days after admission (7 days after symptom onset), and clarithromycin was discontinued.

Lumbar puncture on day 9 after symptom onset showed 10 mononuclear cells/µL (normal <5 cells/µL), protein 476 mg/l (150–450 mg/l), glucose 3.5 mmol/l with a CSF:blood glucose ratio of 0.9 (>0.6) and lactate 2 mmol/l (<2.1 mmol/l). A brain MRI revealed nonspecific leukoencephalopathy.

Blood and urine cultures, collected on admission before antibiotic therapy and repeated after 3 days of persistent fever, remained sterile.

Serological testing performed on days 4 and 11 after symptom onset was negative for tick-borne encephalitis virus, *Borrelia burgdorferi* sensu lato, *Coxiella burnetii*, *Rickettsia rickettsii/conorii/typhi, Francisella tularensis, Treponema pallidum, Mycoplasma pneumoniae* and HIV.

The patient's general and neurological condition improved on the day following onset of doxycycline therapy, with complete clinical recovery within 3 days. Meropenem was discontinued, and doxycycline was switched to oral administration to complete a 14-day course. The patient was discharged home after a 10-day hospital stay (12 days after symptom onset).

At follow-up, the patient reported "brain fog" characterised by marked asthenia and balance disturbance for 6 months, while subjective concentration difficulties persisted for 1 year. Neuropsychological testing was normal.

In the absence of any microbiological documentation of another infectious cause, including common tick-borne diseases, human granulocytic anaplasmosis was retrospectively considered in this immunocompromised patient with acute febrile illness, outdoor activities associated with a high risk of tick exposure and rapid clinical response to doxycycline. On day 4 after symptom onset, blood IgG antibodies against *Anaplasma phagocytophilum* were negative (titre <1:64). IgG seroconversion (titre 1:512) was observed in a convalescent serum collected 6 weeks later (Immunofluorescence Assay, FOCUS Diagnostics, Cypress, CA, USA / Diasorin, Saluggia, Vercelli, Italy). The 8-fold increase in IgG antibody titre confirmed the diagnosis of acute human granulocytic anaplasmosis according to the case definition proposed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [7].

As human granulocytic anaplasmosis had not initially been considered, neither a peripheral blood smear nor *A. phagocytophilum* blood PCR was performed during the acute phase. LDH was not determined. Unfortunately, no stored blood was available for retrospective microscopic assessment of morulae in granulocytes or for *A. phagocytophilum* PCR.

The timeline of key clinical, diagnostic and therapeutic events is summarised in table 1.

Table 1: Timeline of key clinical, diagnostic and therapeutic events.

Time points after symptom onset	Clinical course	Key findings	Clinical assessment and management
Day 0–1	Symptom onset.	High-grade fever, chills, generalised weakness, headache and dizziness.	Initial symptoms preceding hospital admission.
Day 2	Hospital admission.	Temperature 39.9 °C; remaining vital signs normal. Leucocytes 14.4 g/l (neutrophils 10.3 g/l), CRP 22 mg/l.Urinalysis showed leucocyturia, proteinuria and bacteriuria.	Initial diagnostic work-up: suspected UTI.Empirical ceftriaxone.
Day 4	Persistent fever.	Persistent high-grade fever, chills, no clinical infectious focus.Blood and urine cultures of day 2 negative.	Persistent high fever of undetermined origin.Empirical escalation to piperacillin/tazobactam.
Day 5	Persistent fever.	Persistent high-grade fever, chills, new dry cough.	Persistent high fever with suspected atypical respiratory pathogen.Empirical escalation to meropenem plus clarithromycin.
Day 7	Persistent fever.Neurological deterioration.	Persistent high-grade fever, chills.Somnolence, dysarthria, ataxia and fluctuating diplopia.History of summer outdoor activities with a high risk of tick exposure.Blood and urine cultures of day 2 and blood cultures of day 5 negative.	Intracellular or tick-borne pathogen suspected.Empirical intravenous doxycycline 100 mg twice daily.Clarithromycin stopped.
Day 9	Resolution of fever.Neurological improvement.	Afebrile.Awake, neurological improvement.CSF: 10 mononuclear cells/µL, protein 476 mg/l, normal glucose ratio and lactate.MRI: nonspecific leukoencephalopathy.Serologies of day 4 negative for *Borrelia burgdorferi, tick-borne encephalitis virus, Francisella tularensis, Rickettsia spp.* and *Coxiella burnetii.*	Prompt clinical response to doxycycline therapy.Documented mild inflammatory CNS involvement.
Day 10	Clinical cure.	Afebrile.Complete resolution of dysarthria, ataxia, diplopia.	Clinical cure with doxycycline therapy.
Day 12	Hospital discharge.	Afebrile.Marked asthenia, mild dizziness, concentration difficulties.Cultures of day 2 and 5 negative.	Meropenem stopped.Doxycycline orally 100 mg twice daily for a total of 14 days.
Day 16	Outpatient follow-up	Serologies on day 11 negative for *Borrelia burgdorferi, tick-borne encephalitis virus, Francisella tularensis, Rickettsia spp.* and *Coxiella burnetii.*	Microbiological diagnosis unknown.
6 weeks	Diagnosis of human granulocytic anaplasmosis retrospectively considered.	Serology for *A. phagocytophilum* IgG retrospectively tested:Day 4: titre <1:64 (negative)Day 42: titre 1:512 (seroconversion)	Confirmation of human granulocytic anaplasmosis by seroconversion.

Discussion

We report a case of severe human granulocytic anaplasmosis acquired in Switzerland, confirmed by high-titre IgG seroconversion, in an older immunocompromised patient with likely tick exposure [8, 9].

Epidemiological studies show that human granulocytic anaplasmosis is an emerging infection in many European countries [2, 3]. According to the European Centre for Disease Prevention and Control (ECDC), climate change is associated with an increase in tick-borne diseases over recent decades [10]. This trend reflects multiple climate-sensitive eco-epidemiological factors, including expansion of the geographic, altitudinal and seasonal distribution of ticks' activity, changes in natural animal host populations, and human behaviours at risk for tick exposure. Increased diagnostic awareness and improved epidemiological surveillance may also have contributed to this evolving epidemiology [10].

In Switzerland, models suggest that areas suitable for Ixodes ricinus activity increased from 16% to 25% of the national territory over a 10-year period [11]. A. phagocytophilum was detected in 1.7% of ticks [5], supporting the risk of local human exposure. A sero-epidemiological study among Borrelia burgdorferi-seropositive patients in Switzerland reported antibodies against A. phagocytophilum in 17% of participants, suggesting previous exposure in this selected population at high risk for tick-borne diseases [12]. Only one human case acquired in Switzerland has been reported so far [6], suggesting that human granulocytic anaplasmosis may be underdiagnosed.

Whole-blood PCR (Msp-2 gene amplification) is the most sensitive method (>95%) for the early diagnosis of human granulocytic anaplasmosis, especially during the first week after symptom onset [13]. A positive PCR result may guide antibiotic treatment. PCR sensitivity may decrease after administration of tetracycline antibiotics [1].

During acute human granulocytic anaplasmosis, Giemsa-stained peripheral blood smears may reveal morulae in the cytoplasm of granulocytes. The reported sensitivity of blood-smear examination is 20–60%, particularly before initiation of doxycycline, and depends on examiner expertise [13, 14].

Specific serum antibodies against *A. phagocytophilum* may be absent during the acute phase of infection. Serological diagnosis relies on a 4-fold increase in IgG antibody titre between acute and convalescent serum samples, measured by indirect immunofluorescence assay (IFA), with the convalescent sample collected at least 2 weeks after symptom onset. Reported sensitivity and specificity for human granulocytic anaplasmosis diagnosis by IgG seroconversion are 94–100% and 83–100%, respectively [13, 14]. In our patient, a seroconversion with an 8-fold increase of IgG antibody titre (from <1:64 to 1:512) against *A. phagocytophilum* was observed over 6 weeks using a reference IFA assay. These serological results in a patient at high risk of exposure to ticks and presenting with an acute febrile illness confirmed the diagnosis of human granulocytic anaplasmosis, according to the case definition proposed by ESCMID [7]. While serological cross-reactions with *Rickettsia* spp., *Coxiella burnetii* and *Ehrlichia* species are reported [7], serial serological tests for *Rickettsia spp*. and *Coxiella burnetii* were negative in our case, while ehrlichiosis was not specifically tested for.

Regarding other laboratory findings in human granulocytic anaplasmosis, a recent Mayo Clinic cohort of 465 patients [9] reported the classic laboratory triad of leucopenia, particularly lymphopenia, thrombocytopenia and elevated aminotransferase levels in only 24% of cases. Mild-to-moderate elevations in lactate dehydrogenase (LDH) and CRP were reported in one third of cases, and higher absolute neutrophil counts were associated with hospitalisation. In our patient, mild neutrophilic leucocytosis and mild CRP elevation were present at admission, while platelet count and aminotransferase levels remained normal. Mild lymphopenia developed during hospitalisation.

In the same cohort, headache and altered mental status were reported at presentation in 43% and 8% of cases, respectively, and encephalopathy occurred in 38% of hospitalised patients [9]. The neurological deterioration observed in our older immunocompromised patient was consistent with these clinical descriptions. Tick-borne encephalitis was an important differential diagnosis in the present case report. However, serial tick-borne encephalitis virus serologies remained negative; the typical biphasic course was not observed; and the patient responded promptly to doxycycline therapy.

Rare co-infections of human granulocytic anaplasmosis with other tick-borne pathogens, such as Borrelia spp., Ehrlichia spp. and Neoehrlichia mikurensis, have been described, and their clinical manifestations may overlap [3, 4]. Neoehrlichiosis has been reported in Northern and Central Europe, mainly in immunocompromised patients with B-cell malignancies or inflammatory disorders treated with anti-CD20 antibodies. The disease presents with nonspecific systemic

symptoms. In severe forms, venous thromboembolism or arteritis are distinctive features, while neurological manifestations have not been reported [4]. Based on these clinical differences, neoehrlichiosis seems unlikely in our case, although it was not specifically tested for.

Doxycycline is the first-line treatment for human granulocytic anaplasmosis [15]. Although the optimal duration of antibiotic therapy has not been established in clinical trials, a 10-day course is recommended. In mild human granulocytic anaplasmosis, when doxycycline is strictly contraindicated, rifampicin may be considered an alternative, although supporting clinical data are limited [15]. In the Mayo Clinic cohort, doxycycline was started in hospitalised patients after a median of 5 days after symptom onset; median hospital stay was 3 days and 90-day mortality was below 1% [9]. Early diagnosis and treatment may explain the difference from reported North American case fatality rates of 4–18%; European mortality data remain scarce [2, 9].

In our patient, the absence of an early diagnosis led to sequential empirical escalation of broad-spectrum antibiotics, which were ineffective against human granulocytic anaplasmosis. Doxycycline was started empirically on day 7 after symptom onset because of persistent high fever and progressive neurological deterioration. Clinical improvement was observed within 24 hours, with complete recovery within 3 days. The patient was discharged home after a 10-day hospital stay and completed a 14-day course of doxycycline. During follow-up, he reported persistent "brain fog" for several months despite normal neuropsychological testing. Although similar prolonged post-infectious symptoms have been described following Lyme disease and tick-borne encephalitis, both seem unlikely in our case based on serial negative serological testing.

Conclusion

We report a case of serologically documented human granulocytic anaplasmosis acquired in Switzerland, presenting with persistent fever and predominant central nervous system involvement. This case highlights the need to consider human granulocytic anaplasmosis in patients with acute febrile illness and outdoor activities with a high risk of tick exposure, particularly when no alternative diagnosis is identified. Blood PCR during the acute phase is key for early diagnosis and timely initiation of doxycycline treatment. This may avoid erratic empirical antimicrobial escalation, treatment delay, and severe complications with prolonged hospitalisation. Increased awareness of human granulocytic anaplasmosis among Swiss physicians may improve recognition of this probably underdiagnosed disease and contribute to a better understanding of its epidemiology, clinical spectrum and outcomes in Switzerland.

Notes

Informed consent: Written informed consent was obtained from the patient for the publication of the case report.

Use of AI: The authors declare that no generative artificial intelligence (AI) tools or AI-assisted technologies were used in the drafting, writing or creation of this manuscript.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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