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Case Report

Disseminated *Strongyloides stercoralis* infection diagnosed by metagenomic next-generation sequencing of a cell-free DNA blood sample in a patient with hematologic malignancy in Germany: A case report

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ABSTRACT

Background: Rare infections that are atypical for Central Europe are increasingly relevant due to global migration, climate change, and the widespread use of immunosuppressive therapies. Diagnosing such infections is often delayed or missed entirely because conventional testing relies on prior clinical suspicion and region-specific test panels. Hypothesis-free metagenomic next-generation sequencing (mNGS) offers a promising diagnostic strategy in these cases.

Case Presentation: We report a case of disseminated *Strongyloides stercoralis* (*S. stercoralis*) infection with hyperinfection syndrome in a man undergoing B-cell-depleting lymphoma therapy. The patient presented with gastrointestinal and pulmonary symptoms, weight loss, and eosinophilia. Conventional microbiological and serological testing failed to identify a cause. Diagnosis and relevant bacterial and fungal coinfection were established using mNGS (DISQVER) from blood-derived cell-free DNA. Treatment with ivermectin and albendazole led to rapid clinical improvement, and the patient recovered completely.

Conclusion: This case illustrates the diagnostic challenges posed by rare infections in immunocompromised patients in nonendemic regions. It highlights the growing need for broad, rapid, and hypothesis-independent diagnostic tools such as mNGS, which can play a key role in identifying unexpected pathogens and guiding early targeted therapy in high-risk populations.

Introduction

Infectious diseases caused by rare or geographically atypical pathogens are expected to become increasingly relevant in Central Europe [1]. This trend is driven by several converging factors: global migration, international travel, climate change, and the growing use of long-term immunosuppressive therapies in oncology, hematology, and transplant medicine. While most diagnostic strategies rely on clinical suspicion and targeted testing, this approach is prone to failure when unfamiliar or unexpected pathogens are involved.

Strongyloides stercoralis, the causative agent of strongyloidiasis, is a parasitic nematode endemic to tropical and subtropical regions. In nonendemic areas such as Germany, infections are rarely diagnosed and possibly often overlooked [2], especially in their chronic or subclinical form [1,3,4]. However, in immunocompromised patients, even latent infections can lead to hyperinfection or disseminated disease with a high fatality rate [1,3–5].

This case report describes a patient with hematologic malignancy and disseminated strongyloidiasis, diagnosed through

List of abbreviations: mNGS, metagenomic next-generation sequencing; CT, computed tomography; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; CRP, c-reactive protein; BID, twice daily (from the Latin "bis in die"); CNS, central nervous system; BAL, bronchoalveolar lavage; IFI, invasive fungal infection; EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycoses Study Group.

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metagenomic next-generation sequencing (mNGS) of blood-derived cell-free DNA. The case illustrates both the diagnostic limitations of conventional testing in immunosuppressed hosts and the clinical utility of hypothesis-free, broad-spectrum molecular diagnostics. It also underscores the growing need for awareness and preparedness in dealing with rare infections in nonendemic settings.

Case report

A man in his 60s originating from Iran (last visit 2016, no further stays abroad) with mantle cell lymphoma presented to our emergency department with progressive gastrointestinal symptoms, including nausea, weight loss (7 kg in 3 weeks), bloating, melena, and abdominal pain. He had received prior immunotherapy, including rituximab, ibrutinib, and venetoclax as part of a clinical trial (MCL Elderly III; EudraCT-Nr.: 2020-002935-30). At the time of admission, maintenance therapy with ibrutinib and venetoclax was already paused for 3 weeks due to unexplained worsening of clinical status over the last few weeks. The Last Rituximab application was 6 weeks ago.

On clinical examination, the patient was cachectic and dependent on low-flow oxygen. Laboratory tests revealed elevated c-reactive protein (CRP) (175 mg/l, reference <5 mg/l), hypoproteinemia (albumin 20 g/l, reference range 32-46 g/l), eosinophilia (1.4 × 10^9/l; reference <0,5 × 10^9/l), and profound lymphopenia ($CD4^+$ 215/µl, $CD8^+$ 294/µl, $CD19^+$ 0/µl, absolute lymphocytes 1209/µl). Computed tomography (CT) imaging showed terminal ileitis and bilateral pulmonary ground-glass opacities without *Strongyloides*-specific patterns. Empiric treatment with piperacillin/tazobactam and azithromycin was initiated. Gastroscopy revealed mucosal inflammation with fibrinous exudates but no bleeding source.

Initial microbiological testing, including stool culture, stool and respiratory multiplex polymerase chain reaction (PCR), and serologies for *Strongyloides* and *Schistosoma*, remained negative. Of note, enzyme-linked immunosorbent assay (ELISA)-based serology and real-time PCR testing for *Strongyloides* spp. had to be performed in an external laboratory, resulting in an 8-day delay between sample collection and results. Further stool collection was delayed due to paralytic ileus. On day 6, the patient's condition deteriorated with rising CRP (304 mg/l), lactate dehydrogenase (563 U/l, reference <245 U/l), persistent eosinophilia (2.5 × 10^9/l), and new onset confusion. Suspecting drug-induced pneumonitis/colitis or lymphoma involvement, corticosteroids were started, but clinical status continued to decline. In this setting of clinical deterioration with an obvious infectious cause and the underlying pathogens still unidentified, mNGS of cell-free plasma DNA was performed (DISQVER, Noscendo GmbH), which detected *S. stercoralis* (121 reads) as well as *Enterobacter cloacae* (60 reads) and *Aspergillus fumigatus* (25 reads) with a 3-day turnaround time (day 10-13). Accordingly we received positive results for *Enterobacter cloacae* (10^6/ml) as well as elevated Galactomannan antigen (0,51, reference <0.5 [Index]) from a bronchoalveolar lavage (BAL) sample 1 and 2 days after mNGS findings and even higher Galactomannan antigen in a blood sample collected 3 days after receiving the mNGS results (1.45, cutoff <0.5 [Index]).

High-dose ivermectin (15 mg/day via nasogastric tube, equivalent to 0.2 mg/kg for 73 kg), voriconazole, and meropenem were started immediately (day 13), and corticosteroids were withdrawn. The patient improved rapidly, and stool microscopy (*Baermann* technique) and histopathology from gastric biopsies confirmed *S. stercoralis* larvae 5 days after therapy initiation (Figure 1, day 18). Cerebrospinal fluid analysis was negative (ELISA-based serology and PCR test for *Strongyloides* spp.), but cranial magnetic resonance imaging revealed nonspecific contrast-enhancing lesions, raising suspicion for central nervous system (CNS) involvement. Therefore, albendazole (400 mg BID) was added due to limited CNS penetration of ivermectin. In line with the clinical improvement, the inflammation markers normalized, as did the eosinophil count, albeit with a delay. The patient was discharged in good condition on dual antiparasitic as well as antifungal therapy with weekly outpatient appointments.

Albendazol was discontinued after 2 weeks treatment, and Ivermectin was continued for 8 weeks after complete resolution of all symptoms, repeated negative *Bearmann* tests, normalization of eosinophilia, and a negative mNGS follow-up test. Voriconazole was continued for 10 weeks until normalization of galactomannan levels.

Discussion

This case illustrates several key challenges in the diagnosis and management of rare infections in immunocompromised patients in nonendemic regions. *S. stercoralis* infections are rarely encountered in Central Europe, but global migration and climate change may increase their frequency [1,2]. In patients undergoing long-term immunosuppression, particularly with B-cell depleting agents, latent infections may transform into life-threatening hyperinfection syndromes with high mortality rates [1,3,5].

The clinical presentation in our patient—gastrointestinal symptoms, pulmonary infiltrates, and eosinophilia—was suspicious for a helminth infection [3–5] but overlapped with more common differential diagnoses such as bacterial enteritis, drug-induced pneumonitis, or lymphoma progression. Conventional microbiological testing remained inconclusive: stool diagnostics were delayed by ileus, and serologic tests for *S. stercoralis* were false negative, likely due to complete B-cell depletion following rituximab, ibrutinib, and venetoclax therapy. These limitations are well-documented [3,4,6,7] and underscore the poor sensitivity of standard diagnostic modalities in immunosuppressed hosts. It should also be mentioned that the external laboratory reports a sensitivity of 76% for the *Strongyloides* ELISA test used, which therefore itself involves a significant margin for false negative results. CT imaging remained nonspecific, possibly due to a lack of differential diagnostic consideration and missing experience.

Histopathological detection of helminths in gastric biopsies occurred incidentally and with delay. By contrast, mNGS of cell-free plasma DNA (DISQVER) provided rapid, hypothesis-free identification of *S. stercoralis* along with possible relevant bacterial and fungal co-pathogens. The sequencing result enabled targeted treatment before definitive confirmation by stool microscopy was available. The clinical course also highlights the utility of mNGS in uncovering unexpected infections without relying on prior suspicion or pathogen-specific tests. The possible involvement of the CNS could neither be confirmed nor ruled out with certainty, but the initiation of albendazole therapy led to rapid neurological improvement.

However, the high sensitivity of mNGS and the wide range of pathogens also leads to susceptibility to contamination or irrelevant findings. *Enterobacter cloacae* pneumonia, first diagnosed by the mNGS, could be confirmed by BAL. We considered the *Aspergillus fumigatus* mNGS result as pathogenic, supported by a positive galactomannan test in blood and BAL, even though there was no *Aspergillus*-specific radiological finding. Following EORTC/MSG definition [8], only mycological evidence criteria for possible invasive fungal infection (IFI) was met. So far, fungal mNGS findings are not covered by the IFI definition as their diagnostic value remains uncertain. Considering the presence of a fungal genome in the blood, which signals invasive disease, the low likelihood of contamination, and our centerś experience with over 1000 Disqver tests performed on high-risk patients, we treat for IFI in this setting.

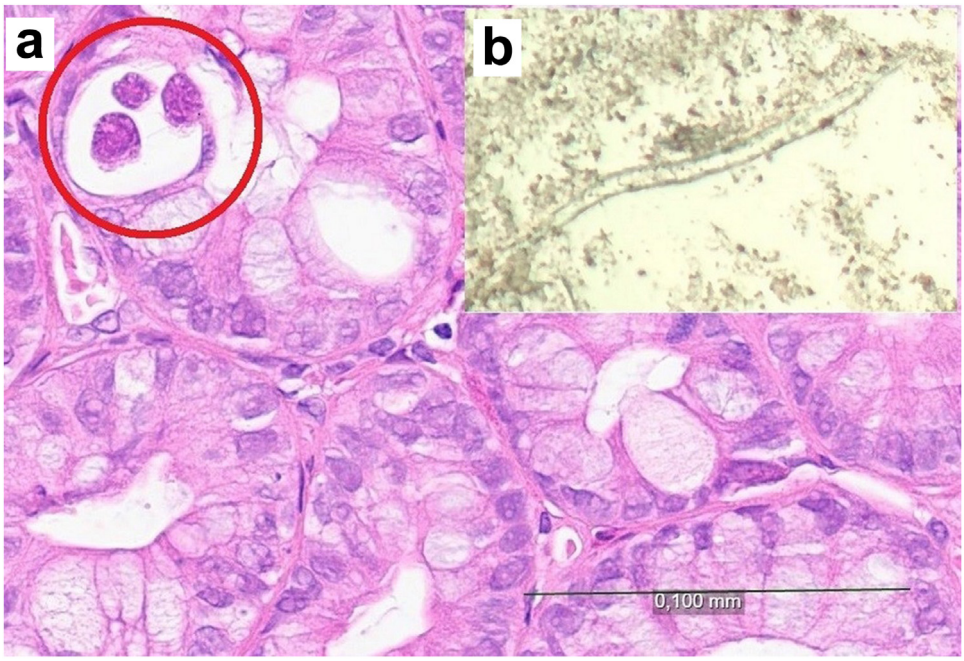

Figure 1. Conventional parasitological diagnostics. (a) Stomach biopsy with intracryptary foreign organisms consistent with a severe helminth infestation (circle). (b) Light microscopic image of a *Strongyloides stercoralis* larva in the patient's stool (Baermann technique).

To our knowledge, preventive screening for high-risk patients is not generally recommended in Germany by existing guidelines. Other countries and societies, such as the American Society for Blood and Marrow Transplantation, recommend screening for specific risk factors and testing of patients at risk for infection [9]. This underscores the lack of awareness of *S. stercoralis* infections in Germany and Europe.

Lacking prospective studies and interpretation guidelines, mNGS requires clinical and infectious disease experience to interpret the findings. Limited, mostly retrospective data of mNGS performance are available in bloodstream and CNS infections [10,11]. Technically, pure germ identification without resistance testing alone may be of limited clinical use. We therefore recommend mNGS as a supplement to, rather than a replacement for, conventional microbiological diagnostics to improve outcomes in high-risk populations.

Conclusion

This case demonstrates the diagnostic complexity of rare infections in immunocompromised patients and underscores the limitations of conventional test strategies. mNGS of cell-free DNA provided rapid, accurate, and actionable identification of *S. stercoralis* in a setting where standard diagnostics failed. As immunosuppressive therapies become increasingly common and global mobility rises, the integration of hypothesis-independent diagnostic tools such as mNGS may be crucial to ensure timely detection and management of uncommon pathogens in this cohort.

Ethical approval and patient consent

Ethical approval was not required for this case report. The patient provided verbal consent for the use of anonymized clinical data and imaging for academic publication. Written consent was waived due to full anonymization and absence of personally identifiable information.

Author contributions

T.M. Möller and O. Kriege managed the patient and drafted the manuscript. G. Hess, M. Dennebaum, and C. Michel contributed to data interpretation, clinical management, and manuscript revision. All authors approved the final version of the manuscript.

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Data availability

Data is available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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