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Strongyloides hyperinfection syndrome due to corticosteroid therapy after resection of meningioma: illustrative case

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BACKGROUND Strongyloidiasis is an underdiagnosed and preventable life-threatening disease caused by infection with the helminth *Strongyloides stercoralis*. Chronic asymptomatic infection can be sustained for decades, and immunosuppression can lead to disseminated infection, with a mortality rate of 70%–100%. In the neurosurgical population, corticosteroids are the most consistent cause of hyperinfection.

OBSERVATIONS The authors present the case of a 33-year-old woman of Paraguayan origin who was diagnosed with sphenoid planum meningioma and treated with a high dose of corticosteroids on the basis of the diagnosis. She underwent surgery, and pathological anatomy reflected grade I meningioma. After the surgery, she started with a history of dyspnea, productive cough, fever, and urticarial rash. Later, she presented with intestinal pseudo-obstruction and bacterial meningitis with hydrocephalus. Serology was positive for *Strongyloides* (enzyme-linked immunosorbent assay), and she was diagnosed with hyperinfection syndrome. Ivermectin 200 μg/kg daily was established.

LESSONS It may be of interest to rule out a chronic *Strongyloides* infection in patients from risk areas (immigrants or those returning from recent trips) before starting treatment with corticosteroids.

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KEYWORDS *Strongyloides stercoralis*; meningioma; corticosteroids; meningitis; hydrocephalus

Strongyloidiasis is a disease caused by infection with the helminth *Strongyloides stercoralis*. This organism is capable of completing its life cycle entirely within the human host. Therefore, a chronic asymptomatic infection can go undetected for decades, and clinical manifestations can occur long after primary infection. In addition, among patients with subclinical infection who subsequently become immunosuppressed, such as in treatment with corticosteroids, larval reproduction can lead to disseminated infection.[1–3]

Because of the widespread use of corticosteroids in neurosurgery (e.g., chronic subdural hematoma, brain tumor, inflammatory pain, hypopituitarism) for long periods (before surgery, during the perioperative period, and after the surgery), it is important in neurosurgical practice to know the risk factors, epidemiology, and management to avoid delays in diagnosis and prevent the high mortality that this disease entails.[4,5]

We report a case of *Strongyloides* hyperinfection syndrome in a patient diagnosed with a large sphenoid planum meningioma and treated with corticosteroids.

Illustrative Case

A 33-year-old woman of Paraguayan origin who had been living in Spain for several years was referred to the emergency department of our hospital by her primary care physician. She had a 1-month history of headache with nausea and vomiting and progressive loss of visual acuity. She had bitemporal hemianopsia in the campimetry. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain with contrast enhancement were performed, and a 3-cm suprasellar mass that compressed the optic chiasm was observed, suggesting a sphenoid planum meningioma

ABBREVIATIONS CSF = cerebrospinal fluid; CT = computed tomography; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; MRI = magnetic resonance imaging.

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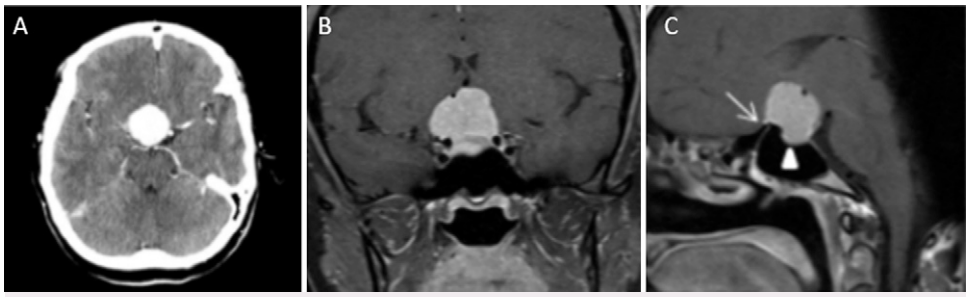

FIG. 1. Expansive suprasellar lesion that spares the pituitary gland (*arrowhead*) and presents with a dural tail (*arrow*), compatible as a first possibility with sphenoid planum meningioma. Axial head CT with contrast (**A**). Preoperative coronal (**B**) and sagittal (**C**) T1-weighted MRI scans with contrast.

as the first possibility (Fig. 1). A course of corticosteroids (dexamethasone 4 mg/8 hours) was started for 21 days. She underwent surgery using a transsphenoidal endoscopic approach. Pathological anatomy reflected grade I meningioma.

Two weeks after surgery, she returned to the emergency room with a history of dyspnea, productive cough with yellowish expectoration, and fever. On examination, she had bilateral pulmonary wheezing and a serpiginous urticarial rash on the trunk and root of her extremities. Her full blood count indicated that the eosinophil and neutrophil counts were within the reference ranges. She was admitted to the hospital with the diagnosis of respiratory sepsis, and antibiotic treatment was started.

Seven days later, she presented with diffuse abdominal pain with nausea and bilious vomiting, and she was diagnosed with intestinal pseudo-obstruction. Also, hypo-osmolar hyponatremia (Na 124 mmol/L) was observed, which was diagnosed as syndrome of inappropriate antidiuretic hormone.

Ten days later, she reported oppressive holocranial headache with nausea and nonbilious vomiting and vision loss with bilateral areactive mydriasis. Under suspicion of pituitary apoplexy, urgent noncontrast MRI was performed, and this reflected multiple restriction foci compatible with areas of ischemia (Fig. 2). Cerebrospinal fluid (CSF) was turbid and showed protein 105 mg/dL (normal range, 10–45), glucose 30 mg/dL (normal range, 50–75), and 1.500/mL polymorphonuclear neutrophlis (normal range, 0–5).

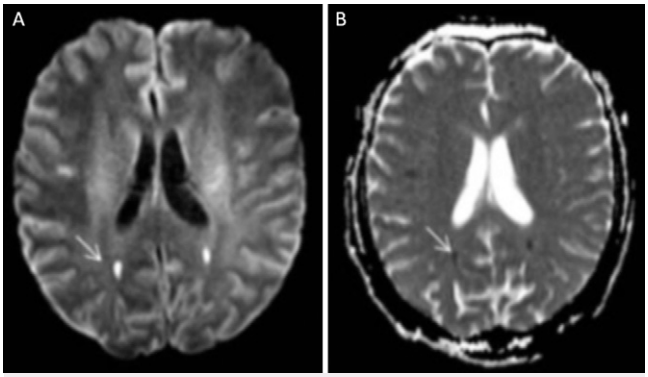

FIG. 2. Axial noncontrast MRI. Bilateral small foci of diffusion restriction compatible with acute ischemia in the deep white matter (*arrows*). **A:** Diffusion-weighted sequence (*b* = 1,000). **B:** Apparent diffusion coefficient map.

She was admitted to the intensive care unit and started with work of breathing, hypotension, and low level of consciousness. For this reason, she was sedated and intubated. Blood cultures showed positive results for *Escherichia coli* and *Klebsiella*. She was diagnosed with septic shock from gram-negative bacteria.

On withdrawal of sedation, she persisted with a low response to stimuli. In the cranial CT, marked dilation of the cerebral ventricular system was observed, compatible with communicating hydrocephalus, probably secondary to meningitis (Fig. 3). External ventricular drainage was performed at right Kocher's point.

Serological test results were positive for *Strongyloides stercoralis* (immunoglobulin G [IgG] positive). The stool and sputum test results were positive, too. The CSF test result was positive for gram-negative bacteria. Treatment with ivermectin (200 μg/kg per day) was started.

She had a good response to treatment, with negative results of all the cultures after the treatment. A ventriculoperitoneal shunt was performed. From the neurological point of view, the improvement was slight. She showed spontaneous eye opening and obeyed simple commands, but fluctuations in the level of consciousness persisted, with a tendency to somnolence. Two months later, the patient died of multiorgan failure.

Discussion

Observations

The importance of knowing this pathology lies in its high prevalence: The estimated strongyloidiasis prevalence is 8.1%, which

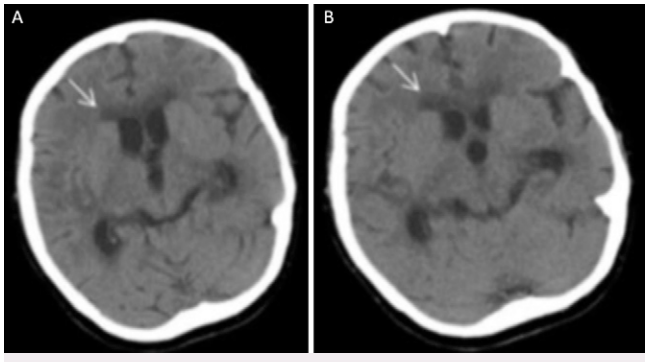

FIG. 3. Axial noncontrast head CT. Marked dilatation of lateral ventricles with periventricular hypodensity, in keeping with transependymal edema (*arrow*), compatible with communicating hydrocephalus.

corresponds to 614 million people infected worldwide (higher than previously reported).[1,2]

Strongyloidiasis is endemic in rural areas of tropical and subtropical regions, where prevalence may exceed 25%. People infected are mostly distributed in Southeast Asia, sub-Saharan Africa, and Latin America (these areas account for three-fourths of all infections).[2,3] The case patient was from Panama, a tropical region located in southeastern Central America.

Strongyloidiasis also occurs occasionally in temperate areas, such as North America, Southern Europe, Japan, and Australia.[2,3] The prevalence of strongyloidiasis among migrants from endemic areas to regions with low endemicity is 12% (the pooled strongyloidiasis seroprevalence)[4–6] (Fig. 4).

The most common route of transmission is via skin contact with contaminated soil. Lack of adequate sanitation facilities is an important risk factor.[7]

The beginning of the life cycle is the contact of the human skin with the filariform larvae of *S. stercoralis*, which are found in soil contaminated with human stool (usually via the feet when people walk barefoot).[8] We think that the patient in our case was contaminated in her native country through her skin.

Once the filariform larvae have penetrated the skin, they migrate to the lungs through the blood and lymph. The larvae ascend the tracheobronchial tree and are swallowed into the gastrointestinal tract. Upon reaching the small bowel mucosa, they develop into adult female worms, which produce eggs that hatch into rhabditiform larvae, which, in turn, are passed in the stool to start the free-living cycle.[7–9]

However, an autoinfective cycle may be established if the rhabditiform larvae develop into filariform larvae within the bowel and the host is reinfected by the invasion of the intestinal wall or perianal skin.[8,9] This peculiar cycle leads to chronic infection (allows the perpetuation of the infection through the years without further exposure). For this reason, disseminated infection can occur in immunocompromised patients.[7–9] The immunosuppression of the case patient was produced by corticosteroid treatment, which is the most frequent cause of immunosuppression in the neurosurgical population.[9,10]

Regarding clinical manifestations, the initial infection is asymptomatic in more than 50% of the cases. Several symptoms have been described, among them the urticarial serpiginous rash of the point of entry the larvae into the skin, as well as cough and tracheal irritation due to the larvae ascending several days later.[11,12] Once the infection is established in in the small intestine (around the third week after transmission), gastrointestinal symptoms such as diarrhea, abdominal pain, or anorexia may occur.[11,12] The case patient had no known history of *Strongyloides* infection, so we suspect that her primary infection was asymptomatic or paucisymptomatic.

Chronic infection is also asymptomatic and may present mainly cutaneous, pulmonary, or digestive symptoms.[10–12] For this reason, it is important to ask about the place of origin and recent travel before starting corticosteroid treatment.

Hyperinfection syndrome refers to accelerated autoinfection with an increased larval migration within the organs normally involved in the autoinfection cycle (e.g., skin, gastrointestinal tract, and lungs).[7,12,13] The case patient started with cutaneous symptoms (serpiginous urticarial rash), followed by pulmonary symptoms (dyspnea, productive cough with expectoration) and abdominal symptoms (diffuse abdominal pain, nausea, and nonbilious vomiting).

The most common risk factor for developing *Strongyloides* hyperinfection syndrome is corticosteroid use.[10–13] For this reason, several series show recommendations to perform screening tests before starting corticosteroid treatment in endemic areas. However, they do not emphasize the necessary duration of corticosteroid treatment.[10–13] Moreover, they do not clarify the approach to be taken in nonendemic areas.

In addition, the migration of filariform larvae during autoinfection may facilitate entry of enteric microorganisms (most frequently gram-negative bacilli) into the systemic circulation. Clinically, this may manifest as extraintestinal bacterial infection such as pneumonia, meningitis, or sepsis; therefore, the presence of fever and/or hemodynamic instability should prompt evaluation for systemic bacterial infection.[12,13]

Meningitis is hypothesized to result from penetration of the blood–brain barrier by larvae as a result of disseminated *Strongyloides* infection.[13,14] This entity can also cause bacterial meningitis; it facilitates the entry of gram-negative bacteria by damaging the intestinal mucosa, and these can cross the blood–brain barrier.[12–14] Hydrocephalus is a severe complication occurring in about 5%–12% of adult bacterial meningitis cases (frequently communicating hydrocephalus due to alterations in the absorption of cerebrospinal fluid) and is an independent risk factor for death and unfavorable outcome.[15]

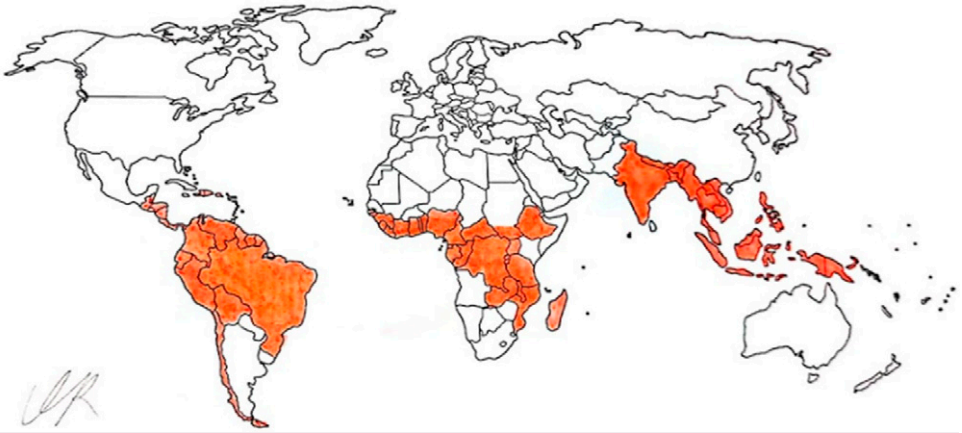

FIG. 4. Most prevalent areas of strongyloidiasis worldwide: Latin America, sub-Saharan Africa, and Southeast Asia.[2,3,6]

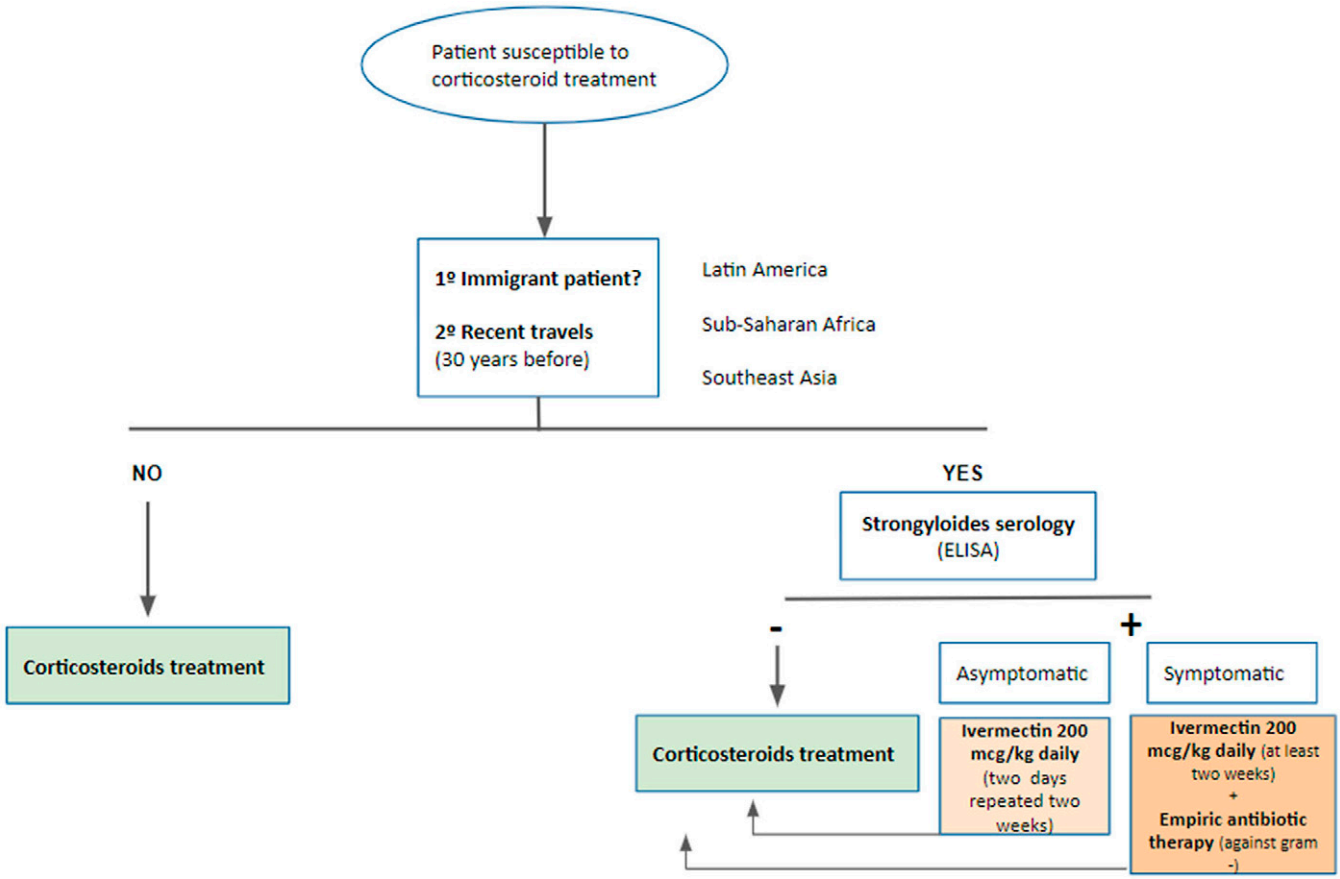

FIG. 5. Management algorithm proposed by our team.

Strongyloidiasis should be suspected among patients with relevant epidemiological exposure (e.g., skin contact with contaminated soil in tropical and subtropical regions) and gastrointestinal, respiratory, and/or dermatologic manifestations, especially if they are under immunosuppressive treatment.[7,8]

In the context of chronic infection, eosinophilia may be observed in approximately two-thirds of cases in the presence or absence of symptoms.[16] However, the sensitivity of eosinophilia for strongyloidiasis is low. Peripheral eosinophilia is usually absent in the context of hyperinfection syndrome.[7,9,16] For this reason, the case patient blood count indicated that the number of eosinophils was normal.

Laboratory tools for diagnosis of strongyloidiasis include stool testing and serology. For patients with dermatologic manifestations, respiratory manifestations, and/or eosinophilia (in the absence of gastrointestinal symptoms), serological testing is recommended; for patients with gastrointestinal symptoms and/or patients with suspected hyperinfection syndrome, serological testing and stool testing are recommended.[17,18]

Serological tests (antibody detection via enzyme-linked immunosorbent assay [ELISA]) have a high negative predictive value, which is useful for the exclusion of *S. stercoralis* infection. This test has high sensitivity (~85%) and specificity (97%) for the diagnosis of chronic infection. The case patient was diagnosed by ELISA, with positive IgG for *Strongyloides*.[17,18]

Regarding management, anthelmintic treatment is recommended for symptomatic and asymptomatic individuals, regardless of immune status. The goal of treatment is to cure the infection, to prevent the development of severe disease in the context of chronic autoinfection[19,20] (Fig. 5).

In uncomplicated infection, treatment with ivermectin is recommended: a single dose or two doses for immunocompetent patients and four doses for immunocompromised patients. The response rate is 85%.[3,19,20]

In patients with known or suspected hyperinfection, treatment with ivermectin (200 μg/kg per day) should be initiated, as should empirical antibiotic therapy with activity against enteric gram-negative bacteria. In addition, patients receiving immunosuppressive therapy should have these regimens reduced, if feasible. The optimal duration of anthelminthic therapy for hyperinfection/disseminated strongyloidiasis is uncertain; treatment for at least 2 weeks is recommended.[3,19,20] The case patient was treated with ivermectin (200 μg/kg per day) for 2 weeks.

Among patients with hyperinfection, the mortality rate is up to 70%–100%. Factors that increase the likelihood of mortality include concomitant immunosuppression, bacteremia, and delayed diagnosis.[3,21]

Serological screening of asymptomatic individuals for strongyloidiasis is warranted in patients with relevant epidemiological exposure (e.g., skin contact with contaminated soil in tropical and subtropical regions) who are undergoing medical interventions associated with immunosuppression (including solid organ transplant, hematopoietic stem cell transplant, or administration of corticosteroids, immunosuppressive drugs, or tumor necrosis factor inhibitors).[21–23] Several series report its

systematic performance in endemic countries, but sometimes the low level of economic resources in those countries does not make it possible.[23,24]

For screening asymptomatic patients with suspected chronic infection, we favor serological testing; stool testing is not sufficiently sensitive.[22,23] For asymptomatic patients who are embarking on immunosuppressive therapy, it is recommended to perform serological testing followed by prompt administration of empirical treatment (ivermectin 200 μg/kg daily for 2 days, repeated at 2 weeks).[24]

Lessons

Corticosteroid treatment is the most frequent cause of hyperinfection in patients with previous undiagnosed chronic strongyloidiasis. This is especially relevant in neurosurgical patients, who frequently receive steroids to minimize cerebral edema.

Having an initial suspicion is very important because, in the absence of early diagnosis and treatment, the prognosis of disseminated strongyloidiasis is extremely poor (rate of mortality 70%–100%).

It may be of interest to rule out a chronic *Strongyloides* infection in patients from risk areas (immigrants or recent travelers from Latin America, sub-Saharan Africa, or Southeast Asia) before starting treatment with corticosteroids. *Strongyloides* serology (ELISA) could be performed before starting corticosteroids, and ivermectin treatment should be instituted when necessary.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Pérez-López, Rodríguez Domínguez. Acquisition of data: Rodríguez Domínguez, Vivancos Sánchez. Analysis and interpretation of data: Pérez-López, Rodríguez Domínguez, Isla Guerrero. Drafting the article: Pérez-López, Rodríguez Domínguez, Isla Guerrero, Abenza Abildúa. Critically revising the article: Pérez-López, Rodríguez Domínguez, Vivancos Sánchez, Utrilla Contreras. Reviewed submitted version of manuscript: Rodríguez Domínguez, Vivancos Sánchez, Utrilla Contreras, Isla Guerrero. Administrative/technical/material support: Vivancos Sánchez, Isla Guerrero.

Supplemental Information

Previous Presentations

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