Systemic infection with Alaria americana (Trematoda)

B.J. FERNANDES, MD; J.D. COOPER, MD, FRCS(c); J.B. CULLEN, MD, FRCP(c); R.S. FREEMAN, PH D; A.C. RITCHIE, MB, FRCP(c); A.A. SCOTT, MD, FRCP(c); P.F. STUART, MD, FRCP(c)

Alaria americana is a trematode, the adult of which is found in mammalian carnivores. The first case of disseminated human infection by the mesocercarial stage of this worm occurred in a 24-year-old man. The infection possibly was acquired by the eating of inadequately cooked frogs, which are intermediate hosts of the worm. The diagnosis was made at autopsy. The mesocercariae were present in the stomach wall, lymph nodes, liver, myocardium, pancreas and surrounding adipose tissue, spleen, kidney, lungs, brain and spinal cord.

There was no host reaction to the parasites. Granulomas were present in the stomach wall, lymph nodes and liver, but the worms were not identified in them. Hypersensitivity vasculitis and a bleeding diathesis due to disseminated intravascular coagulation and a circulating anticoagulant caused his death 8 days after the onset of his illness.

L'Alaria americana est un trématode dont la forme adulte est retrouvée chez les mammifères carnivores. Le premier cas d'infestation disséminée chez l'humain attribuable au méosocercaire de ce ver est survenu chez un homme de 24 ans. Il est possible que l'infestation alt été acquise par l'ingestion de grenouilles insuffisamment cuites; celles-ci servent d'hôte intermédiaire à ce parasite. Le diagnostic a été posé de la vie du patient par biopsie pulmonaire et il a été confirmé à l'autopsie. Les méosocercaires étaient présentes dans la paroi stomacale, les ganglions lymphatiques, le foie, le myocarde, le pancréas et les tissus adipeux environnants, la rate, les reins, les poumons, le cerveau et la moelle épiplâtre. On n'a constaté aucune réaction de l'hôte envers le parasite. Des granulomes étaient présents dans la paroi stomacale, les ganglions lymphatiques et le foie, mais on n'a pu déceler aucun ver à l'intérieur. Une vascularite allergique et une diathèse hémorragique causée par une coagulation intravasculaire disséminée et un anticoagulant à action générale ont entraîné la mort 8 jours après le début de la maladie.

Species of the trematode Alaria are frequently found in Ontario. Their definitive host is a carnivore, such as a wolf, coyote, fox, lynx, bobcat, marten or skunk. From this definitive host the life cycle of the alariae takes them is often delayed greatly even when the presence of congenital heart defects indicates the possibility of the condition. Extracardiac manifestations predominate. Pneumonia or meningitis or both in a susceptible patient merit consideration of endocarditis. The pneumonia is likely to be embolic in origin, as in our patient, in whom it should have led to an earlier diagnosis. Atypical early manifestations may mislead the physician to pursue unrelated disorders. Because of the changing and variable clinical patterns, a high index of suspicion in a susceptible patient population is essential for a prompt diagnosis. In the present case the inordinate delay of diagnosis was due to a fragmented approach to patient care, in which reliance on laboratory investigations displaced the inherent values of a comprehensive and careful approach based on history and physical findings.

References
into two intermediate hosts — first a snail, then a tadpole. The trematodes persist in the frogs that develop from the infected tadpoles. The life cycle is completed when a definitive host eats an infected tadpole or frog. The stage of the trematode that infects the definitive host is called a mesocercaria. The mesocercariae of the alariae can also infect paratenic, or nonessential, hosts, such as other frogs, garter snakes, domestic chickens, house mice, deer mice, ferrets and raccoons. In such hosts the mesocercariae survive but do not develop into the adult form of the worm, as they do in a definitive host.

One case of infection of the retina of the human eye by the mesocercaria of a species of Alaria has been reported. No case of disseminated human infection has been described in the literature. We report a case of widespread infection by mesocercariae identified as A. americana.

Case report

Clinical summary
A 24-year-old man was admitted to the Belleville (Ont.) General Hospital with severe respiratory failure and was transferred a few hours later to the respiratory care unit of the Toronto General Hospital. The patient worked as a welder in Toronto but the family had a summer farm near Belleville. He often went on long hikes and camping trips and had hiked near the farm during the weeks preceding his illness. There was no history of significant previous illness.

Two days before admission he experienced malaise and vague abdominal pain. On the day of admission, cough, shortness of breath and hemoptysis developed. The dyspnea rapidly increased in severity and necessitated his admission to hospital.

He was acutely ill, with a temperature of 39°C, and was sweating profusely. His respiratory rate was 45/min; pulse rate, 160 beats/min; and blood pressure, 100/90 mm Hg. Small, flat, nonpalpable purpuric spots were numerous on the face, trunk and legs; there were no nodules. Subcutaneous emphysema extended over the anterior chest wall and into the neck. Bilateral, diffuse rales were heard in the lungs.

Chest radiograph showed a diffuse nodular infiltrate in the lungs, with mediastinal and subcutaneous emphysema (Fig. 1). Blood gas values while he was breathing 100% oxygen (12-l flow delivered through a face mask) with spontaneous ventilation were as follows: Pao2, 40 mm Hg; Paco2, 26 mm Hg; pH, 7.60. Hemoglobin value was 12.7 g/dl and leukocyte count, 14.0 x 10^9/l with 93% polymorphs, 2% lymphocytes, 2% monocytes and 3% bands. There was no eosinophilia. Blood urea nitrogen, blood glucose and serum electrolyte values were normal. Shortly after his admission to Toronto General Hospital an endotracheal tube was inserted and positive-pressure ventilation was begun.

A skin biopsy showed acute hypersensitivity vasculitis affecting small vessels, as did a second biopsy 1 day later. A subsequent open lung biopsy revealed hemorrhagic spots, 1 to 3 cm in diameter, covering the surface of the lung. Serial sectioning of the biopsy over the next 2 days revealed a single fluke, lying without inflammation in the grossly hemorrhagic pulmonary parenchyma (Fig. 2). The fluke was subsequently identified as the mesocercarial stage of a species of Alaria.

The patient was given broad-spectrum antibiotics and steroids. He also received bithionol (an anthelmintic) by nasogastric tube. He failed to respond to therapy, remaining severely hypoxic in spite of mechanical ventilation with positive end-expiratory pressure and high oxygen concentration. In addition, a bleeding diathesis developed due to disseminated intravascular coagulation, as shown by thrombocytopenia (platelet count, 90 x 10^9/l) and an increase in concentration of circulating fibrin/fibrinogen degradation products (to more than 160 mg/ml). A circulating anti-coagulant with heparin-like activity also appeared in his blood.

On the 4th hospital day therapy with a membrane oxygenator was instituted because the Pao2 was persistently less than 40 mm Hg in spite of maximal ventilatory assistance and an Pao2 of 1.0. On the 5th day the patient suddenly became hypotensive (systolic blood pressure, 70 mm Hg). He showed no spontaneous or reflex movements. Intracranial hemorrhage was suspected. The following day, after 48 hours' perfusion with the oxygenator, an electroencephalogram showed no electrical activity. The patient remained hypotensive (systolic blood pressure, 35 mm Hg) in spite of an epinephrine drip and he died on the 6th hospital day.

Autopsy findings

Many purpuric hemorrhages, from 3 cm in diameter to pinpoint, were scattered over the skin of the entire body. Subcutaneous emphysema extended over the anterior chest wall and into the neck. Extensive but patchy hemorrhage was noted in almost all viscera.

The pericardial cavity contained 60 ml of yellow, serous fluid. The pericardium appeared normal. Hemorrhages 2 to 5 mm in diameter were scattered throughout the myocardium (Fig. 3).

The right pleural space contained 50 ml of hemorrhagic fluid and the left, 40 ml. The pleural surfaces were hemorrhagic. The right lung weighed 2290 g and the left, 1600 g; the cut surfaces were dark purple, with diffuse hemorrhage in all lobes.

The peritoneal cavity contained 300 ml of hemorrhagic fluid. The wall of the stomach was greatly thickened by blotchy hemorrhagic lesions, evident from both mucosal and serosal surfaces. Numerous submucosal and subserosal hemorrhages appeared throughout the small intestine; in some areas transverse strips of dark purple alternated with unaffected yellowish-gray bowel. Many ecchymotic hemorrhages were present in the mesentery and adjacent adipose tissue.

The liver weighed 2290 g. The lining of the intrahepatic portal veins was shaggy and irregular. The pancreas and adrenal glands contained focal hemorrhages; the kidneys, multiple punctate hemorrhages in the parenchyma and focal hemorrhages in the pelvis; and the testes, patchy interstitial hemorrhage.

Diffuse, recent subarachnoid hemorrhage, scattered petechiae in the cortex and white matter of the brain and spinal cord, and intracerebral hematomas in the left anterior temporal lobe and both frontal lobes were noted. The cerebral hemispheres were diffusely swollen.
Microscopic findings

Seven types of pathologic reaction were noted.

1. Hemorrhage: Recent interstitial hemorrhage was present in all organs but was particularly prominent and massive in the lungs, gastrointestinal tract and brain.

2. Thrombi: Fibrin thrombi were present in the capillaries of the glomeruli and heart. Larger thrombi were seen in veins in the liver, lungs, heart and stomach; in the portal veins of the liver many of the thrombi showed early organization.

3. Focal necrosis: Many organs contained small foci of parenchymal necrosis; they were particularly numerous in the heart. Some were the tracks left by the worms as they crawled through the tissues (Fig. 4); others seemed related instead to the vasculitis or thrombi. Sometimes a neutrophil reaction was associated with the necrosis but frequently there was little reaction. In the liver, eosinophils were sometimes prominent in the foci of necrosis.

4. Inflammation: Granulomas composed of macrophages, foreign body giant cells, eosinophils and lymphocytes were seen in the liver, lymph nodes and stomach wall. In the liver they were mainly in the portal areas; other triads showed only eosinophils. In lymph nodes there was sinus histiocytes and edema; large multinucleated giant cells were prominent in the sinusoids and in the parenchyma (Fig. 6). They were also noted in the wall of the stomach (though they were not numerous in spite of the intense inflammation), in the myocardium, pancreas and surrounding retroperitoneal adipose tissue, spleen, kidney, lungs, brain and spinal cord. In none of these sites was there an inflammatory reaction immediately around the organism. The trematodes caused no inflammation as they burrowed through the tissues, even though at times they could be seen at the end of the tunnels they had formed. Even in organs such as the stomach, lungs and lymph nodes, in which there was extensive inflammation, the inflammatory changes were not in relation to the identifiable organisms.

5. Vasculitis: The skin showed a low-grade, chronic vasculitis with lymphocytic cuffing of vessels in the superficial dermis. Necrotizing arteritis was evident in only a few small arteries and arterioles in the kidney and liver.

Discussion

So far as we know, this is the first example of generalized infection with the mesocercariae of *A. americana* in man. The parasitologic aspects of the case will be discussed in more detail elsewhere.

Since alarial mesocercariae cannot multiply in the human body, the patient must have ingested the several thousand mesocercariae estimated to have been present at autopsy. Because of the extensive thickening of the stomach wall with pronounced inflammation, it is assumed that this was the site of entry of the parasites into the tissues. The source of the infection has not been established, but probably the patient ate inadequately cooked frogs' legs. One frog's leg can harbour thousands of alarial mesocercariae.

The parasites probably spread both by direct passage through the tissues and by the lymphatics, as the many organisms in the retroperitoneal adipose tissue and the large numbers in lymph nodes suggest. The ineffectiveness of the patient's response to the parasite is evident from the large numbers of motile parasites isolated at autopsy and the lack of an inflammatory reaction to them in most organs.

The migratory patterns of the mesocercariae in paratenic and final hosts is not clearly established, but in paratenic hosts they disseminate widely and frequently concentrate in the adipose tissue. All the flukes recovered from the patient were mesocercariae, which suggests that their further development to the diplostomulum, or adult, probably did not occur, although organisms in such stages were not sought in the lumen of the intestine at autopsy.

In the tadpole and adult frog the mesocercariae are encysted either in masses or singly. The wall of the cyst is composed of collagen, which becomes hyalinized. The contents may be either gelatinous or fluid, with motile meso-
cercariae. The cellular reaction may consist of scant macrophages, polymorphs and foreign body giant cells. Only in the stomach and lymph nodes of our patient was there pronounced inflammation; minor changes were noted in the liver. Despite extensive serial sectioning, parasites could not be demonstrated in the areas of inflammation. It is likely that some substance produced by the parasites excited the reaction as they migrated through the gastric wall, but why it engendered an inflammatory response there and not elsewhere is not clear. Perhaps the gastric wall was most affected because all the parasites probably passed through it before becoming disseminated throughout the body.

This patient’s clinical course was attended by two major complications: a coagulation abnormality and hypersensitivity vasculitis.

At autopsy, evidence of intravascular coagulation was seen in the form of platelet and fibrin microthrombi in capillaries which were responsible for the massive hemorrhage in almost every tissue. The existence of a generalized immunologic reaction in this patient was first suggested by his purpura and was confirmed by the skin biopsy, which showed acute vasculitis. At autopsy acute vasculitis was seen in small arteries and arterioles in the kidney and liver. Immunofluorescent staining of the kidneys did not demonstrate abnormal deposition of immunoglobulins, but trace amounts of fibrin were present in the glomeruli. Presumably the immunologic reaction and the bleeding tendency were responsible for the massive pulmonary and cerebral hemorrhage, which were major factors in this man’s death. No doubt the immunologic reaction was a response to some product derived from the mesocercariae, perhaps because some earlier infection had established sensitization.

Further studies are in progress in an attempt to isolate an antigen from the parasite and to establish its relation to the vasculitis and pulmonary hemorrhage.

The only other case of Alaria mesocercarial infection reported was in a patient from the same area. It would be interesting to see whether unexplained granulomas or Alaria mesocercariae can be found in tissues from routine autopsies conducted in this and nearby areas.

References

Prescribing information
Beclovent®

INDICATIONS
1. Treatment of steroid-responsive bronchial asthma.
2. Prevention of asthma in patients who are steroid-dependent but whose condition warrants such treatment.

CONTRAINDICATIONS
1. True or drug-allergic reaction to Beclovent Inhaler. Do not use in patients who have had asthma reactions to components of the Beclovent Inhaler.
2. Patients with an active systemic infection who are not responding to antiviral therapy may not be candidates for Beclovent Inhaler therapy.

PRECAUTIONS
1. It is essential that patients be informed that Beclovent Inhaler is a preventive agent, must be taken at regular intervals, and is not to be used during an asthmatic attack.
2. The replacement of a systemic steroid with Beclovent Inhaler has to be gradual and carefully supervised by the physician, the guidelines under Dosage and Administration should be followed in such cases.
3. Unscheduled administration of drugs during the first trimester of pregnancy is undesirable. Concomitant use of other drugs may need to be continued throughout pregnancy.
4. In patients previously on high doses of systemic steroids, abrupt discontinuation of Beclovent Inhaler may cause withdrawal symptoms such as transient fever, headache, and joint pain. A decreased resistance to infection has been observed during corticosteroid therapy. During long-term therapy, supplemental-alphabetic function and hemostatic status should be periodically assessed.
5. Fluconazole propionates may be hazardous if they are administered dose four times in the daily high amount of Beclovent Inhaler. Thus, the dose may need to be increased, and the dose may need to be decreased if hypokalemia is noted, and if possible, sodium should be added to the daily high amount of Beclovent Inhaler. This is of special importance in the treatment of systemic corticosteroid therapy.
6. In patients with hypothyroidism and in those with corticosteroid therapy, Beclovent Inhaler may cause exacerbations of symptoms.
7. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

ADVERSE REACTIONS
1. No major adverse effect attributable to the use of Beclovent Inhaler has been reported. In general, minor mild and transient effects have been observed when the daily dose was below 200 mcg (four puffs). Above this dose, reduction of systemic corticosteroid, indicating exacerbation of the symptoms, may occur. These symptoms may cause the appearance of Candida albicans in the mouth and throat.
2. The replacement of systemic steroids with Beclovent Inhaler has been associated with cases of systemic diabetes, of hy- pokalemia, and of hypotension, which were major factors in deceased during corticosteroid therapy and may become apparent during Beclovent Inhaler therapy.

SYMPTOMS AND TREATMENT OF OVERDOSE
Overdose may cause systemic symptoms such as adrenal suppression and hypokalemia. Decreasing the dose will abolish these side-effects.

DOSAGE AND ADMINISTRATION
The optimal dosage of Beclovent Inhaler may vary widely and must be individually determined, but the total daily dose should not exceed 1 mg of beclomethasone dipropionate (20 puffs).

Children: Overdosage information is available to warrant the safe use in children under six years of age. The average daily dose for children under six years of age is 0.5 mg/kg of body weight.

I M P O R T A N T
As a steroid aerosol, Beclovent Inhaler is for maintenance therapy. It is not indicated to give immediate relief and is not recommended for use in the treatment of acute exacerbations of asthma or in the management of acute attacks. In such cases, the patient should be transferred to more intensive treatment, including the temporary resumption of systemic steroids. The development of pharyngeal and laryngeal candidiasis is a common symptom of Beclovent Inhaler treatment. The development of candidiasis can generally be held to a minimum by having patients rinse their mouth with water after each inhalation.

PRECAUTIONS
1. These precautions and the directions for use, which is intended to give immediate relief and is not indicated for use in the treatment of acute exacerbations of asthma.
2. The development of pharyngeal and laryngeal candidiasis is a common symptom of Beclovent Inhaler treatment. The development of candidiasis can generally be held to a minimum by having patients rinse their mouth with water after each inhalation.

SUPPLIED
Beclovent® Inhaler is a metered-dose aerosol delivering 100 mcg (2 puffs) of beclomethasone dipropionate per puff. There are two hundred doses in a container. Official product monograph is available on request.

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