

### Case 1

Ali Zaidi, H.B.Sc. (OT7), Faculty of Medicine, University of Toronto  
Rajkumar Vajpeyi, MD, Faculty of Medicine, University of Toronto

#### History

**M**rs. M., a 69 year-old woman, was referred to the gastroenterology clinic by her family doctor with a two-week history of cramping abdominal pain, watery and bloody diarrhea, tenesmus, fatigue, and fever under 37.5°C for most days. The symptoms started mildly, and gradually worsened over that period of time. She had some relief of the abdominal pain and fever with acetaminophen. Mrs. M. had recently returned from a visit to Pakistan four weeks prior. Her past medical history was remarkable for coronary artery disease, a possible mild myocardial infarction (MI) and coronary artery bypass graft 11 years ago, and occasional reflux. Her regular medications included omeprazole 20 mg po qid, acetylsalicylic acid 75 mg od and atenolol 50 mg bid.

#### Physical

Vital signs were normal, with a low-grade fever (37.1°C). Abdominal examination elicited mild lower abdominal tenderness on deep palpation. Digital rectal examination was normal.

#### Investigations

Hb = 119 (115 - 160 g/L)  
WBC = 7 (4.0 - 11.0  $\times 10^9$ /L)  
Plt = 297 (150 - 400  $\times 10^9$ /L)  
MCV = 95.6 (80 - 98 fL)  
ESR = 50 (<20 mm/hr)  
AST = 35 (8 - 35 U/L)  
ALT = 31 (8 - 40 U/L)  
ALP = 57 (40 - 130 U/L)  
Albumin = 37 (30 - 50 g/L)  
Bilirubin (total) = 9.3 (2 - 14 mmol/L)  
Bilirubin (direct) = 2.5 (0 - 4 mmol/L)  
Fecal occult blood = positive  
Fecal leukocytes = negative  
Urinalysis = normal

Stool microscopy was ordered. Gastroscopy was normal. Colonoscopy revealed severe ulceration in the cecum (Figure 1.1). Multiple biopsies of these lesions were taken, and select images are shown (Figure 1.2a-c).

**What is the diagnosis?**

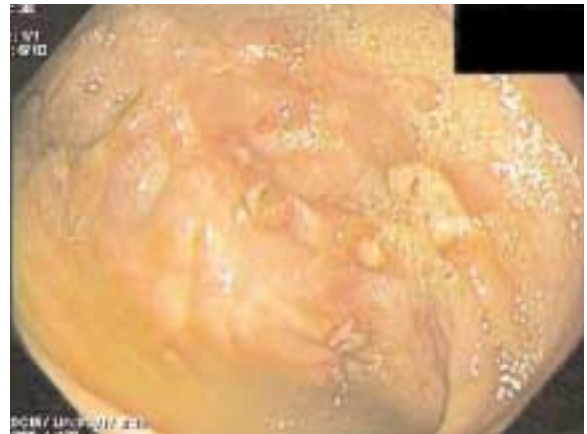


Figure 1.1. Cecal ulceration seen on colonoscopy.

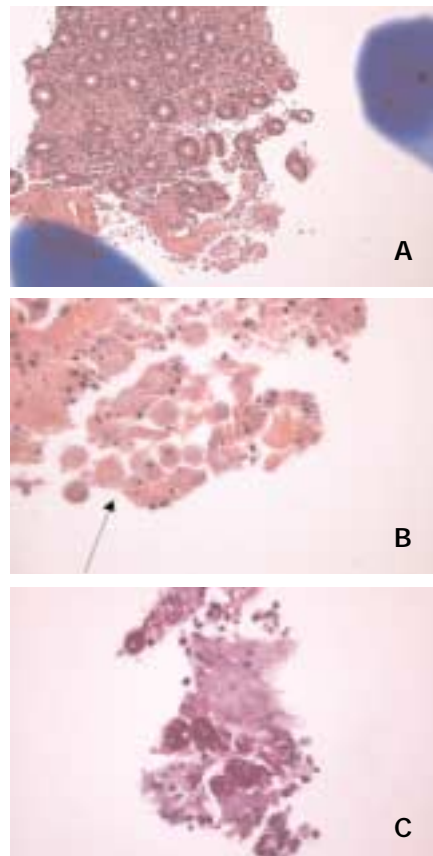


Figure 1.2. Hematoxylin and eosin (H & E)-stained slides of colonoscopy biopsy sample. A. Mucosal ulceration in the colon, blue ink is around area of ulceration. B. Trophozoites containing ingested red blood cells. C. Periodic Acid Schiff (PAS) positively stains the trophozoites.

## Case 2

Tom Trajkovski, H.B.Sc. (OT7), Faculty of Medicine, University of Toronto  
 Peter Ferguson, MD, M.Sc., FRCSC, Division of Orthopaedic Surgery, Mount Sinai Hospital; Department of Surgical Oncology, Princess Margaret Hospital

**A** 16 year-old previously healthy male presented to his family physician's office after suffering an injury to his hip while golfing. He reported no other musculoskeletal complaints at the time. Functional inquiry was unremarkable. Past medical history was significant for asthma. He was taking no medications at the time, and his only drug allergy was codeine. He denied smoking and alcohol use. Physical exam was unremarkable.

Radiographs of the hip were normal. A bone scan (Figure 2.1) was obtained, and it showed no evidence of increased uptake in the hips; however, there was significant uptake in the right humerus. A radiograph (Figure 2.2) showed evidence of a large sclerotic lesion in the mid-diaphysis of the humerus. The patient denied having any pain in his arm.

The patient was lost to follow-up, but presented to the emergency department ten months later with a three-week history of right arm swelling and worsening shoulder pain. He endorsed pain at rest. His pain was worst at night and was not relieved with NSAIDs. He had decreased appetite during this time, but no weight loss, fever, or night sweats. He denied any history of trauma. He had otherwise been well. Review of systems was unremarkable.

On examination, the patient was a Native American gentleman weighing approximately 230 pounds. He was afebrile and his vital signs were stable. Cardiovascular examination was normal. Bilateral crackles were present on auscultation of the lung fields. A large mass was present on the upper two thirds of his right arm. The mass was firm and fixed. There was no tenderness to palpation. There was no evidence of axillary lymphadenopathy. Range of motion of the shoulder was slightly limited, with loss of 10 degrees of forward flexion and abduction. He endorsed no pain with range of motion testing. Neurovascular examination showed a mild decrease in motor function of the radial nerve, thumb extension (4/5); otherwise, motor function of the deltoid, biceps, triceps, finger abductors, and finger flexors were 5/5 and symmetrical. Sensory examination showed evidence of decreased sensation in the axillary nerve distribution. Brachial artery and radial artery pulses were strong. Capillary refill was less than two seconds. The rest of the musculoskeletal examination was normal.

X-rays were obtained. (Figure 2.3)

**What is the diagnosis?**



Figure 2.1. Total body Technetium-99m bone scan showing increased uptake in right humerus.



Figure 2.2. Lateral radiograph of right humerus. Note marked sclerosis within intramedullary canal.



Figure 2.3. AP radiograph of right humerus shows a large blastic lesion with evidence of extensive periosteal reaction and associated soft tissue mass.

## And the diagnosis is . . .

### Case 1

#### Diagnosis: Amoebic Dysentery

#### Etiology and Epidemiology

Amoebiasis is one of the three most common causes of death from parasitic disease after malaria and schistosomiasis, and is caused by the protozoan, *Entamoeba histolytica*.<sup>1,2</sup> Although it is prevalent worldwide, developing countries have high prevalence rates due to low socio-economic conditions and poor sanitation levels.<sup>1,3</sup> Globally, approximately 40 to 50 million people develop colitis or extraintestinal disease annually, with 100,000 of these cases resulting in death.<sup>1,2,4</sup> Areas that have particularly high rates of amoebic infection include India, Africa, Mexico and parts of Central and South America.<sup>1,4</sup> Although infection with *Entamoeba dispar* is almost ten times more common than infection with *E. histolytica*,<sup>1,4</sup> *E. dispar* is non-pathogenic and does not cause clinical disease.<sup>1</sup> However, *E. histolytica* is not a common cause of traveler's diarrhea.<sup>1,4</sup> Prevalence of amoebic infection might be as high as 50% in some developing areas, and is about 4% in developing countries overall.<sup>1,2,4</sup> In developed countries, amoebiasis is mostly seen in immigrants from and travelers to endemic areas, institutionalized patients, sexually-active homosexuals, and HIV-positive individuals.<sup>1,2,4</sup>

#### Pathogenesis

The primary reservoir for *E. histolytica* is humans and the major route of transmission is through contaminated fresh food or water.<sup>3,4</sup> Another route of transmission is oral-anal sexual contact.<sup>3</sup>

*E. histolytica* exists in two forms: the infective cyst and the multiplying invasive trophozoite.<sup>3,4</sup> The cysts can survive outside the host for weeks to months, but are quickly destroyed at temperatures below -5°C and above 40°C.<sup>2</sup> Infection occurs via ingestion of the infective cysts (only one is sufficient to cause disease), which pass from the stomach to the terminal ileum, where they excyst to form daughter trophozoites. In 90% of infections, the trophozoites re-encyst to produce asymptomatic infection, which usually subsides spontaneously within 12 months. In the remaining 10%, symptomatic amoebiasis develops.<sup>4</sup> The trophozoites are motile and extend cytoplasmic projections, called pseudopodia to engulf food particles and red blood cells. They invade intestinal epithelial cells, causing tissue destruction and enhanced intestinal secretion, leading to bloody diarrhea.<sup>1,3,4</sup> They can also spread through the bloodstream, causing extra-intestinal lesions, mainly liver abscesses.<sup>3,4</sup> The incubation period can last from two days to four months.<sup>4</sup> The trophozoite of *E. histolytica* can convert back into a cyst form by going through a precyst stage in the large intestine. The cyst is then excreted in stools, thereby restarting the cycle.<sup>3</sup>

The pathogenicity of amoebic trophozoites is related to their binding to intestinal epithelial cells by a specific lectin

(the galactose/N-acetylgalactosamine lectin),<sup>1</sup> and lysis of target cells through a variety of molecules, including proteases, adhesins and amoebapores.<sup>1,3,4</sup> During the invasive phase, mucosal IgA antibodies are produced.<sup>4</sup> Mucosal immunity against the lectin appears to provide some protection from invasive disease.<sup>1</sup> Antigen-specific responses lead to the production of lymphokines, such as interferon- $\gamma$ , which mediate the macrophage response against the trophozoites.<sup>4</sup> Cell-mediated immunity plays an important role in limiting the disease and providing protection against recurrences.<sup>4</sup> Although asymptomatic *E. histolytica* infection is able to invoke an antibody response, infection with *E. dispar* is not.<sup>4</sup>

#### Clinical Picture

As noted above, the majority of *E. histolytica* infections are either asymptomatic or associated with very mild symptoms.<sup>1,2</sup> Risk factors for development of severe disease and increased mortality include young age (especially neonates), pregnancy, malignancy, corticosteroid use, malnutrition, and alcoholism.<sup>1,4</sup>

Symptomatic intestinal amoebiasis usually presents with a subacute onset of one to three weeks. The symptoms range from mild diarrhea to severe dysentery (proctocolitis) with abdominal pain and bloody diarrhea.<sup>1</sup> Patients with dysentery typically have colic pain. Although weight loss occurs in about one-fifth of patients<sup>2</sup> and fever in about 8 to 38%,<sup>1</sup> systemic manifestations are generally absent. These presentations can be differentiated from diarrhea of bacterial origin, where patients frequently display systemic signs and symptoms, such as fever, chills, headache, anorexia, nausea and vomiting.<sup>3</sup>

Characteristic colonic features vary from thickening of the mucosa to the classic flask-shaped ulcers (Figure 1.3), which predominantly occur in the cecum or the appendix.<sup>2</sup> Less commonly, localized chronic colonic infection can result in a mass of granulation tissue called an amoeboma, which can be mistaken for colon cancer.<sup>1,4</sup> Other rare intestinal complications include perianal cutaneous lesions, rectovaginal fistulae, and toxic megacolon.<sup>1,2</sup> Although it occurs in only 0.5% of cases, fulminant colitis with necrosis, perforation, and peritonitis carries a mortality rate of about 40 to 50%.<sup>1,4</sup>

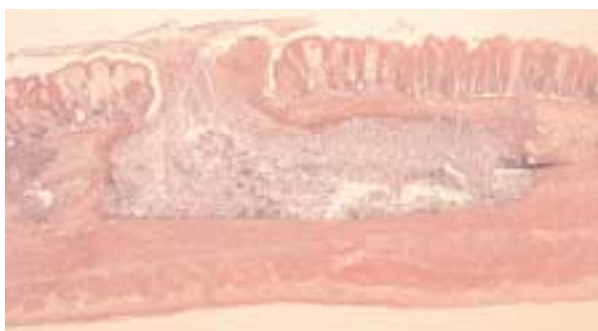


Figure 1.3. Typical flask-shaped intestinal ulcer (not from case). (Reproduced with permission from Microbiology and Immunology Online, University of South Carolina, <http://pathmicro.med.sc.edu/parasitology/intest-protozoa.htm>).

The most common extraintestinal manifestation of amoebiasis is liver abscess.<sup>2,4</sup> Liver abscess occurs ten times more frequently in adults and males compared to children and females, respectively.<sup>2,4</sup> In uncomplicated cases, the mortality rate is less than 1%.<sup>4</sup> Approximately 10% of patients with amoebic liver abscess also develop pleuropulmonary amoebiasis.<sup>4</sup> Other rare complications include peritonitis, pericarditis and cerebral amoebiasis, a rapidly fatal condition.<sup>4</sup>

With regards to laboratory investigations, leukocytosis can occur, but eosinophilia is not seen. ESR is usually elevated.<sup>4</sup> Liver function tests demonstrate elevated alkaline phosphatase (ALP) in 80% of cases, elevated transaminases, and reduced albumin levels.<sup>4</sup> Stool analysis in the acute state commonly shows presence of Charcot-Leyden crystals, lack of fecal leukocytes, and presence of blood.<sup>2</sup>

Differential diagnoses that should be considered in cases of amoebiasis include infectious causes, such as *Campylobacter*, *Shigella*, *Salmonella*, *Yersinia*, enteroinvasive *Escherichia coli*, enterohemorrhagic *Escherichia coli*; and non-infectious causes, such as inflammatory bowel disease, ischemic colitis, diverticulitis, and arteriovenous malformation.<sup>4</sup>

## Diagnosis

The diagnosis of invasive amoebiasis can be achieved by a combination of methods, such as stool examination, serological testing, and colonoscopy and biopsy of intestinal lesions.<sup>2</sup> Presence of cysts or trophozoites on stool microscopy suggests intestinal amoebic infection.<sup>1</sup>

Multiple techniques exist to differentiate between *E. histolytica* and *E. dispar*, including antigen and DNA detection enzyme immunoassays (EIA) and PCR.<sup>2</sup> Some consider EIA to be the best clinical test for diagnosing *E. histolytica*.<sup>4</sup> Several antigen detection assays to differentiate *E. histolytica* from *E. dispar* are now commercially available.<sup>1</sup> Serological tests are also useful, as antibodies can be detectable in 75% to 85% of patients with symptomatic *E. histolytica* infection within five to seven days.<sup>1,2</sup> Although indirect hemagglutination (IHA) is the most sensitive assay to detect antibodies, it is not useful in differentiating between acute and previous infection, since antibodies can persist for years after resolution of disease.<sup>1,4</sup>

Although some consider stool microscopy to be less sensitive than antigen testing,<sup>1</sup> one way to differentiate *E. histolytica* from *E. dispar* microscopically is the presence of erythrophagocytosis (Figure 1.2).<sup>2</sup> This finding is considered diagnostic for *E. histolytica* in patients with dysentery, and has long been considered a classical diagnostic feature.<sup>2</sup>

Sigmoidoscopy and especially colonoscopy are valuable tools for visualizing mucosal inflammation and typical ulcers covered with yellowish exudates, as well as obtaining scrapings and biopsy specimens.<sup>1,4</sup> Ultrasound and CT are employed in cases of amoebic liver abscess and cerebral amoebiasis, respectively.<sup>4</sup>

## Treatment and Prevention

It is recommended that individuals who are asymptotically colonized with *E. histolytica* be treated, as cyst carriers can be infectious and may develop disease after some time.<sup>2</sup> This is especially important for patients with AIDS.<sup>4</sup> In areas where amoebic infections are endemic, asymptomatic patients with stools positive for amoebae are presumed to be

infected with *E. dispar*, and are usually not treated. This practice might change once reliable tests to differentiate between *E. histolytica* and *E. dispar* are more readily available in resource-poor countries.<sup>1</sup>

Antibiotic treatment of intestinal amoebiasis is aimed at eradicating the invasive trophozoites and the intestinal carriage of the organism. Metronidazole is considered to be the drug of choice for symptomatic invasive amoebiasis.<sup>4</sup> Metronidazole treatment (500 to 750 mg po tid in adults, and 35 to 50 mg/kg per day in three divided doses for children, for seven to ten days in both) has cure rates of approximately 90%.<sup>1</sup> Moreover, resistance to this drug has not been reported.<sup>1</sup> Paromomycin is considered to be the drug of choice for non-invasive disease.<sup>4</sup> Other drug treatments include tinidazole, ornidazole, chloroquine, and dehydroemetine (for in-patient use).<sup>1</sup> Follow-up stool examinations are required after completion of therapy.<sup>1</sup>

Treatment of peritonitis generally includes broad-spectrum antibiotics. Surgery is indicated if significant bowel perforation is present, or if non-responsiveness to antibiotics with development of abscess following perforation develops. The one absolute indication for surgery is toxic megacolon, which is treated with total colectomy.<sup>1,4</sup> Amoebic brain abscess and pericardial involvement of amoebic liver abscess also require surgical treatments.<sup>4</sup>

Prevention strategies for travelers to endemic areas include avoiding unboiled or unbottled water, uncooked food, and fruits and vegetables that may have been washed with local water. There is some evidence of acquired partial immunity against amoebic infection. Work on vaccine development is currently ongoing.<sup>1</sup>

## Back to the Case

Stool microscopy before gastroscopy/colonoscopy revealed presence of amoeba. Antimicrobial treatment with metronidazole 750 mg po tid was initiated for a ten-day course. In light of the patient's previous history of possible MI and coronary artery disease, she was asked for a repeat CBC (to ensure stable Hb) before returning for a follow-up in two weeks. Post-treatment stool examination was also arranged.

## Acknowledgements

We would like to thank Dr. George Therapondos for providing us with the clinical details of the case and the colonoscopy images.

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## And the diagnosis is . . .

### Case 2

#### Diagnosis: Osteoblastic Osteosarcoma

##### Epidemiology

Primary malignant tumours arising from the skeletal system are rare, representing just 0.001% of all new cancers.<sup>1</sup> Aside from multiple myeloma, osteosarcoma is the most common primary malignant tumour of bone. Global incidence is thought to be between 1-3 per million people annually.<sup>2</sup> It is the third most common cancer in adolescents, occurring less frequently than only lymphomas and brain tumours.<sup>3</sup> The majority of patients who develop osteosarcoma are in their second decade of life, and males and females are affected equally. Although this tumour can occur in any bone, the appendicular skeleton is most frequently involved, with approximately 50% of lesions occurring about the knee. The distal femur is the most common site, followed by the proximal tibia and the proximal humerus. Multifocal involvement is extremely rare.<sup>3</sup>

##### Etiology

The exact etiology of osteosarcoma is unknown. However, rapid bone growth appears to predispose to osteosarcoma, as suggested by the increased incidence during the adolescent growth spurt. Bone dysplasias, including Paget's disease, fibrous dysplasia, and bone infarcts are considered to be predisposing factors. Environmental factors, such as exposure to radiation have also been implicated in the formation of osteosarcoma.<sup>4</sup> Several hereditary risk factors are also known to predispose to osteosarcoma. Hereditary retinoblastoma, associated with germline mutations in the RB gene, is associated with a 100-fold increase in the development of osteosarcoma.<sup>5,6</sup> The Li-Fraumeni syndrome is associated with germline mutations in the p53 tumour suppressor gene, and also with an increased risk of osteosarcoma. In view of these genetic predisposition syndromes, it is not surprising that RB and p53 are frequently found to be mutated in many patients with osteosarcoma. Numerous studies have found the frequency of p53 mutations to be in the range of 18-30%.<sup>7,9</sup> Alterations in the RB gene appear to be even more common than p53 alterations, with loss of heterozygosity reported in more than 50% of cases.<sup>10</sup>

##### Presentation

Most patients with classic osteosarcoma have symptoms of pain before a mass is noticeable. Symptoms may be present for weeks, months, or even longer before osteosarcoma is diagnosed. Patients may complain of so-called "growing pains" which can further delay diagnosis. The patient often has a history of trauma, although this is not thought to be an etiologic factor. The patient may endorse a history of swelling, depending on the size of the lesion and its location. Systemic symptoms, such as fever and night sweats are rare. Metastases most commonly develop in the lungs and rarely

result in respiratory symptoms. Such symptoms usually indicate extensive lung involvement.<sup>11</sup>

##### Diagnosis

Radiographic evaluation combined with clinical history and histologic examination are necessary for accurate diagnosis. Magnetic resonance imaging (MRI) of the affected bone, computerized tomography (CT) scan of the chest, and a radionuclide bone scan are necessary to delineate local and systemic extents of disease. The radiographic findings of conventional osteosarcoma include permeative lytic destruction of the metaphyseal bone mixed with dense sclerosis due to bony matrix synthesis by the tumour, extensive periosteal reaction, and eventual cortical breakthrough into the subperiosteal space. Malignant tumour cells can then elevate the periosteum and stimulate reactive bone formation. This radi-



Figure 2.4. Radiograph demonstrating characteristic Codman's triangle and sunburst periosteal reaction.



Figure 2.5. Histological specimen of conventional osteoblastic osteosarcoma.

ological sign is often described as Codman's triangle (Figure 2.4). As the tumour continues to push its way into the extra-cortical soft tissue, a typical sunburst pattern of neoplastic bone may be seen outside the involved bone.<sup>3</sup>

The histologic diagnosis of an osteosarcoma depends upon the presence of malignant sarcomatous stroma associated with the production of tumour osteoid and bone. A number of different histologic types of osteosarcoma exist. The largest group of osteosarcomas are the conventional (intramedullary high grade) osteosarcomas, which account for approximately 90% of all osteosarcomas.<sup>12</sup> The conventional type can be subdivided based on the predominant features of the cells (osteoblastic, chondroblastic, fibroblastic). Figure 2.5 illustrates the characteristic findings in conventional osteoblastic osteosarcoma: hyperchromatic, ovoid, and tapered nuclei are present, growing in sheets and forming lace-like osteoid, and thicker woven bony trabeculae with calcification. Occasional cells have marked nuclear pleomorphism, and multinucleated malignant giant cells are noted within the lesion. Focal chondroid areas merge with the osteoid.<sup>3</sup>

Other types of osteosarcoma include the telangiectatic type, which contains large blood-filled spaces and presents commonly in adolescence and early-adulthood. The parosteal type usually arises from the bone cortex and can be seen in childhood or adulthood. It is low grade and most commonly arises on the distal posterior aspect of the femur. Lastly, periosteal osteosarcoma is a very rare tumor that typically arises immediately below the periosteum in children and most frequently involves the tibia.<sup>3</sup>

### Treatment

Before the advent of adjuvant multidrug chemotherapy, the treatment of osteosarcoma was radical amputation. Today, with the combination of chemotherapy and surgical treatment, the five-year survival approaches 70%.<sup>14</sup> Despite the favourable response of osteosarcomas to chemotherapy, surgery is a necessary component of curative therapy.<sup>14</sup> The specific surgical procedure is dictated by the location and extent of the primary tumour.<sup>15</sup> Although all patients with extremity sarcomas are candidates for amputation, emphasis on functional outcome has focused efforts on limb-sparing procedures; however, not all patients are candidates for more conservative surgery. In order to avoid local recurrence, tumour control must be the primary therapeutic concern, and functional outcome a secondary goal.

### Back to the Case

A tissue biopsy was performed; it confirmed the diagnosis of high-grade osteogenic osteosarcoma. CT examination of the chest showed multiple pulmonary nodules consistent with pulmonary metastases. The patient was treated with neoadjuvant chemotherapy, which included doxorubicin, cisplatin, and high dose methotrexate. Surgical management included limb sparing surgery with resection of the entire humerus and reconstruction with allograft and cemented prosthesis. Unfortunately, the patient developed postoperative complications and a shoulder disarticulation was subsequently performed. The patient is currently receiving further cycles of chemotherapy for his pulmonary metastases.

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