Clinical basics

Tuberculosis: 6. Extrapulmonary disease

Education

Éducation

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Tuberculosis (TB) is a systemic infection caused by *Mycobacterium tuberculosis*. It is transmitted by coughed aerosol and usually presents with respiratory symptoms. However, it can produce disease in any organ system. Dissemination from the site of initial infection in the lung can take place at the time of primary infection or years later, when immunologic containment fails.

The practitioner should be aware that TB occurs in sites other than the lungs and that these sites account for an increasing proportion of cases of TB in North America.[1-4] People born in Asia, Africa, Latin America and Oceania or in aboriginal communities of Canada have a high likelihood of infection and a 10% risk of active disease. Immunosuppression due to age, disease or debility, but most particularly due to HIV infection, increases the risk of reactivation and of unusual presentations of TB[5,6] (see subsequent article in this series on TB and HIV).

Epidemiology

The mean annual number of cases of TB in Canada was 2019 over the 5-year interval 1986 to 1990 and 2028 in the subsequent 5-year interval (Table 1).[1] The mean annual number of cases of respiratory TB, which in the Canadian data includes pulmonary, pleural, miliary, primary and other respiratory TB, declined slightly, from 1553 in the first 5-year interval to 1510 in the second 5-year interval. At the same time the mean annual number of nonrespiratory or extrapulmonary cases increased to an equal extent. It should be noted that the category "unknown" was not used until 1989, and after 1989 a small number of cases each year were reported as "site unknown." From 1986-1990 to 1991-1995, no changes occurred in the mean number of cases of abdominal TB, TB meningitis or miliary TB. There was a small increase in the annual numbers of cases of primary TB, lymph node TB and skeletal TB and a 25% reduction in the number of cases of genitourinary TB. The reduction in genitourinary TB coincided with the wide use of quinolones to treaturinary tract sepsis. It is possible that the antituberculous activity of quinolones may have reduced the number of recognized cases of genitourinary TB. The small increase in the proportion of cases that were extrapulmonary may reflect an increased ability to detect extrapulmonary disease or an increase in the survival of immune-suppressed people and the likelihood of TB reactivation at unusual sites. Lymph node TB is the most common form of TB among those under the age of 15 years, whereas skeletal and genitourinary TB increase with increasing age.[3] Miliary and meningeal TB are seen at the extremes of age.

The effect of HIV on the presentation of TB depends on the CD4 lymphocyte count: the lower the count, the greater the likelihood that the presentation of TB will be unusual.[5] Whereas extrapulmonary TB accounts for only 20% of cases of TB in people who do not have HIV, it accounts for 53% to 62% of cases in HIV-seropositive people.[6] The most common extrapulmonary site in those infected with HIV is the lymph node, but pleural, pericardial, intra-abdominal, central nervous system and disseminated forms of TB also occur more frequently in HIV-seropositive people than in those without this type of infection.

Diagnosis

The diagnosis of extrapulmonary TB depends on the physician considering the possibility of TB in patients at risk and submitting material for mycobacterial culture and pathological examination. In the affected tissues, the number of *M. tuberculosis* organisms is small, except if there is caseation or cavity formation. Tissue biopsy yields positive culture results more often than fluid aspiration.[7] The yield of *M. tuberculosis* organisms from any fluid is low, and this yield is lessened by dilution. Urine is most concentrated in the morning; hence, the first-voided specimen is likely to have the highest yield.[8]

The granulomatous lesion is nonspecific, and the differential diagnosis can include atypical mycobacterial infection, fungal infection, sarcoidosis and foreign-body reaction.[9] Langhans giant cells are more suggestive of tuberculous granulomas, but the presence of acid-fast bacilli may represent either typical TB or an atypical mycobacterial infection. Hence, culture is the gold standard for diagnosis. It is possible that a polymerase chain reaction (PCR) probe for genetic sequences originating from the *M. tuberculosis* complex may be helpful, but at present PCR is only reliable in sputum-smear-positive cases.[10] (see subsequent article in this series on the laboratory aspects of TB).

Early in the clinical course, fluid (e.g., pleural, peritoneal or joint) from the affected site will probably exhibit polymorphonuclear leukocytosis, but after 2 weeks lymphocytes predominate. The protein level becomes elevated, and the glucose level diminishes. The level of adenosine deaminase is not diagnostic but tends to be above 60 U/L in patients with TB.[11]

Table 1: Mean annual number of Canadian cases of tuberculosis at pulmonary and extrapulmonary sites in two 5-year intervals (1986–1990 and 1991–1995)*

	Period; mean annual no. of cases†	
Anatomic site	1986–1990	1991–1995
Respiratory		
Pulmonary and pleural	1353	1293
Primary	156	168
Miliary	45	49
Total respiratory	1554	1510
Nonrespiratory		
Lymph node	226	263
Genitourinary	102	71
Skeletal	46	55
Abdominal	28	31
Central nervous system	17	16
Other	35	62
Total nonrespiratory	454	499
Site unknown	12	19
Total	2019	2028

*Source: Statistics Canada and Health Canada data. For the purposes of these data, "respiratory TB" includes pulmonary, pleural, primary and miliary TB, and "non-respiratory TB" includes all other extrapulmonary TB.
†Values were obtained by dividing 5-year totals by 5. Discrepancies between sums and some of the totals presented are due to rounding.

Cerebrospinal fluid is seldom smear positive, and only 50% of samples yield positive cultures.[12] In a patient born in a country where TB is endemic or in a patient of aboriginal ancestry, an elevated leukocyte count, with lymphocytes predominating, a low glucose level and an elevated protein level, along with subacute onset of neurologic symptoms, should alert the physician to the possibility of tuberculous meningitis. In such cases treatment should be initiated promptly, on the basis of clinical suspicion and epidemiologic information; the physician should not await culture confirmation.

The following sections describe extrapulmonary TB and present illustrative cases.

Case 1: Lymph node TB

A 50-year-old aboriginal woman noted an enlarging mass in the right neck over a period of 4 weeks. The mass was firm, slightly tender and associated with fevers and sweats. She was known to have AIDS, and her CD4 count was less than 100×10^9 /L. She had hitherto refused all antiretroviral drugs and isoniazid prophylaxis (see subsequent article in this series on chemoprophylaxis), which had been recommended because she had a history of inadequately treated primary TB. The lymph node was excised, and examination revealed poorly formed granulomata and many acid-fast bacilli, which grew *M. tuberculosis* sensitive to all drugs tested. In spite of advanced HIV disease, she had complete resolution of the lymphadenopathy.

Lymph node TB is seldom complicated by systemic symptoms, except in people with HIV infection, in whom the bacterial load is large.[13,14] The nodes are usually discrete, firm and nontender, but with time they may become fluctuant and drain spontaneously with sinus tract formation. Anterior and posterior triangles of the neck are the most common sites (in 70% of cases), followed by inguinal and axillary sites.[15] The best diagnostic procedure is excisional biopsy, which yields the diagnosis in 80% of cases. In the hands of a surgical expert, fine-needle aspiration biopsy is diagnostic in 60% of cases.[15]

In Canada, atypical mycobacterial lymphadenopathy is much more common than *M. tuberculosis* infection in children under the age of 5 years.

Case 2: Genitourinary TB

A 64-year-old woman reported a 1-week history of fever and left flank pain. She had a history of recurrent cystitis involving mixed bacterial organisms; this condition failed to respond to antimicrobial treatment. Urinalysis showed many poylmorphonuclear leukocytes and erythrocytes. Routine culture was negative, but an early-morning urine sample grew *M. tuberculosis*. Intravenous pyelography showed left hydronephrosis (Fig. 1). Creatinine clearance was normal. Chest radiography showed no evidence of pulmonary TB. The obstructed left ureter required dilatation. Treatment with 4 antituberculous drugs for 2 months and 2 drugs for the next 4 months resulted in resolution of the symptoms. Persistent narrowing of the ureter did not measurably reduce renal function.

Genitourinary TB occurs with the hematogenous spread of tubercle bacilli to the glomeruli. Medlar and associates[16] performed autopsies for 829 people who had died of pulmonary TB and found that 21% of them had glomerular lesions. The infection spreads in the genitourinary tract to involve renal pelvis, ureter, bladder, seminal vesicles, epididymis and testes. It is estimated that it takes between 8 and 22 years to produce a symptomatic renal lesion. Hence, it is a rare occurrence in children.

The symptoms of genitourinary TB are those of bacterial pyelonephritis, recurring in spite of treatment; sterile pyuria is frequent.[17] There may be concomitant pulmonary TB but not invariably. A solitary genital lesion may occur in men, but such a lesion is usually associated with urinary tract symptoms. The genital lesions in women are less often associated with renal disease but present with symptoms of chronic pelvic inflammation.

In an Alberta series of 105 cases of TB with positive urine culture for *M. tuberculosis* diagnosed between 1975 and 1984,[17] symptoms were present in 62% of the patients. The ratio of males to females was 66:39. The most common symptoms were flank pain, nocturia, frequent voiding and dysuria; testicular involvement was present in 16% of cases. The finding of persistent sterile pyuria should suggest renal TB.[18] Because of the risk of reaction to contrast material, intravenous pyelography, which was performed in case 2, has been replaced by ultrasonography for demonstrating obstructive lesions.[19] The definitive diagnosis depends on culture of the urine.

During treatment it is important to follow the patient carefully to ensure patency of the lower collecting system. Ureteral narrowing may require dilatation or stenting to prevent progressive obstruction.

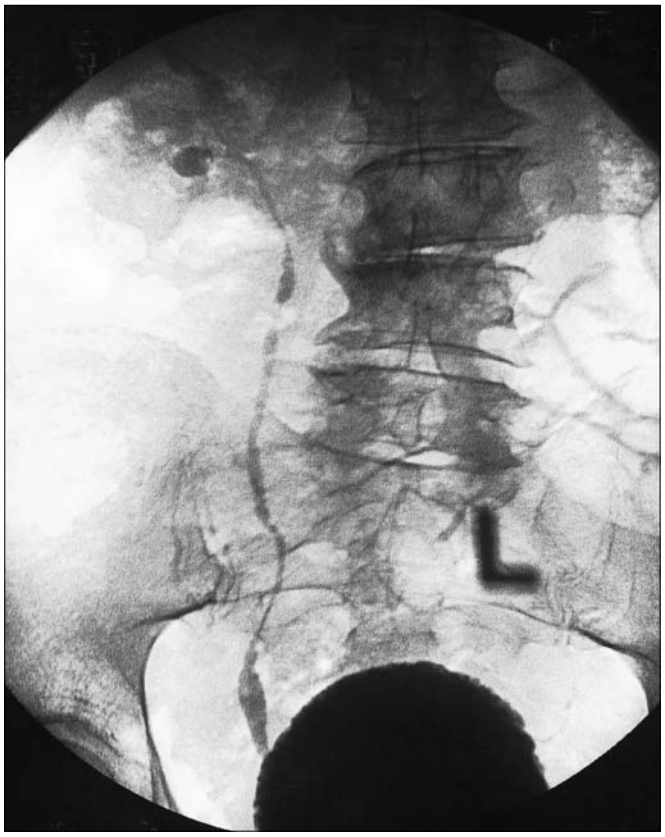

Fig. 1: Case 2. Intravenous pyelogram shows left mid-ureteral narrowing and upper tract dilatation. Lower tract obstruction is common in genitourinary tuberculosis.

Case 3: Skeletal TB

A 40-year-old previously well woman who had immigrated to Canada from Thailand 10 years previously presented with a 4-week history of gradual swelling over the left sacroiliac joint. She had no cough, fever or night sweats and no history of TB. Examination revealed diffuse swelling over the left sacroiliac joint. The skin overlying the area was of normal colour and did not feel warm. The area was tender to palpation. She was afebrile. The results of a neurologic exam were normal except for absence of the left patellar reflex and numbness in the distribution of the fourth lumbar vertebra (L4). A complete blood count was normal. The sedimentation rate was 50 mm/h. The results of chest radiography were normal. Lumbar spine radiographs showed osteomyelitis with narrowing of the L3-L4 joint space. A myelogram showed a space-occupying lesion at L3-L4 (Fig. 2). At surgery an abscess that corresponded to the lesion shown on the myelogram was found and debrided. On direct smear examination of the debrided tissue, acid-fast bacilli were seen. Culture confirmed *M. tuberculosis*.

The patient's pain resolved after the surgery. She completed 6 months of supervised medication with no recurrence.

The spine is the most common site of TB involving the bones, accounting for 50% of cases. The large joints — the hip, knee, shoulder, elbow and wrist — are less com-

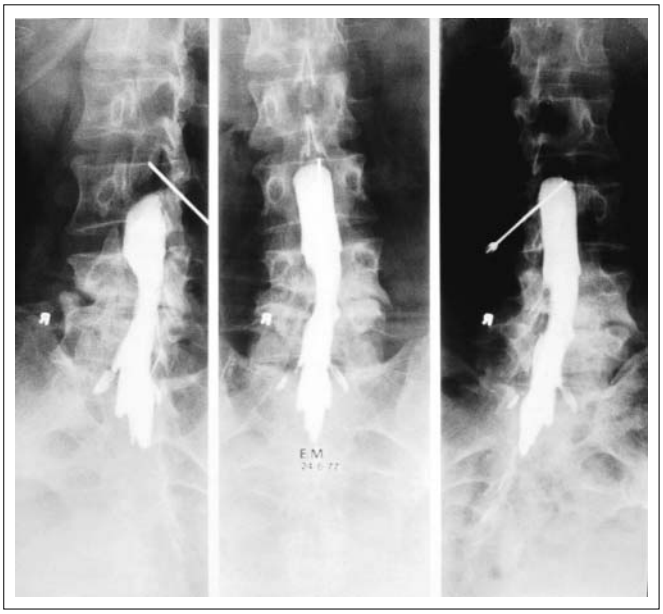

Fig. 2: Case 3. Myelogram shows narrowing of the L3-L4 disk space and osteomyelitis of the adjacent vertebral bodies, as well as a filling defect in the contrast media corresponding to the location of the tuberculous abscess in the spinal canal.

mon sites, and TB of the small joints is rare.[20] The most common symptoms of skeletal TB are pain, tenderness and limitation of motion. About one-third of cases have soft-tissue fluctuance or sinus drainage.[20] The accompanying systemic symptoms may include fever, weight loss and malaise. In most cases the blood count is normal, but the sedimentation rate is usually elevated. The diagnosis depends on biopsy for culture and pathologic examination of the affected tissues, because radiographs are not diagnostic. The tissue surrounding the bony lesion shows granulomatous change, but the bacterial population is usually small, and culture results may be negative.[21]

Although radiographs are not diagnostic, CT helps to target the biopsy site.[21] Bone scans have been reported to give negative results in 35% of cases, and gallium scans in 70% of cases.[22] MRI is the modality of choice, because it can discriminate between abscess and granulation tissue and can delineate soft-tissue masses and identify the amount of bone destruction.[23,24] The differential diagnosis includes other pyogenic infections, which are usually of more acute onset, or other chronic infections such as those caused by fungi, *Nocardia* and *Brucella*.

In regions of the world where TB is common, it has been recommended in cases of suspected bone TB that treatment proceed without culture diagnosis because of the lack of appropriate facilities. However, in developed countries, where TB is less common, culture of a specimen before initiation of therapy is optimal, to confirm the diagnosis and to define the sensitivity of the organism.[21]

Surgery is recommended only for diagnostic biopsy, for patients with unstable or deformed spines, for those whose condition does not improve after 3 to 4 weeks of antibiotic therapy and for those in whom progressive neurologic symptoms develop while they are receiving adequate treatment.

Case 4: Miliary TB

A 30-year-old Canadian-born white man presented to the emergency department with a 1-week history of fatigue and fever. He was mildly short of breath but denied productive cough. He was thin and malnourished. His temperature was 40°C, his blood pressure normal, his heart rate 110 beats/min and his respiratory rate 30/min. The spleen tip was palpable and nontender. No lesions were seen in the retinae. Initial chest radiography results were interpreted as normal, but because of persistent dyspnea, repeat radiography was performed; the image revealed evidence of a diffuse miliary infiltrate (Fig. 3). A tuberculin skin test, with only 4 mm of induration, was interpreted as negative. Because the patient had normochromic, normocytic anemia and a hemoglobin level of 100 g/L, bone marrow biopsy was performed; small granulomata with occasional acid-fast bacilli were observed. Sputum and bone marrow grew *M. tuberculosis* at 3 weeks. The patient responded well to antituberculous treatment initiated after the bone marrow biopsy, but 2 weeks later he reported a 4-cm swelling over the right frontal region of his scalp. Skull radiography showed osteomyelitis, as seen in Fig. 4. The inflammatory lesion can be seen penetrating both plates of bone and causing inflammation of the meninges. Aspirate from a ring-enhancing lesion (not shown) also grew *M. tuberculosis*. After completion of 6 months of supervised medication, he had no neurologic sequelae.

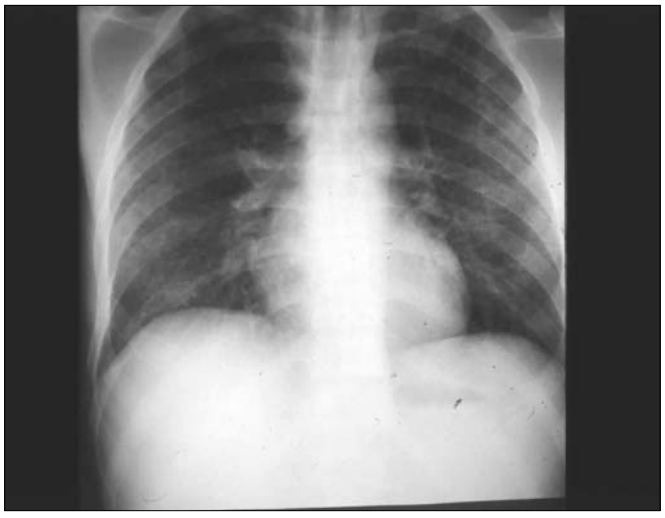

Fig. 3: Case 4. Chest radiograph shows miliary pattern.

The term "miliary TB" refers to the tiny (less than 2 mm in diameter), discrete granulomatous lesions in lungs and other organs that result when blood-borne tubercle bacilli seed many tissues. The common sites include the spleen, the liver, the bone marrow, the kidneys and the adrenal glands, as well as the lungs, but any tissue may be involved. Hematogenously disseminated, *M. tuberculosis* infection may progress at the time of primary infection or years or decades later, at a time of immune suppression.

In North America, miliary TB is most common in elderly people[25] and in HIV-infected patients.[4,6] Immunosup-

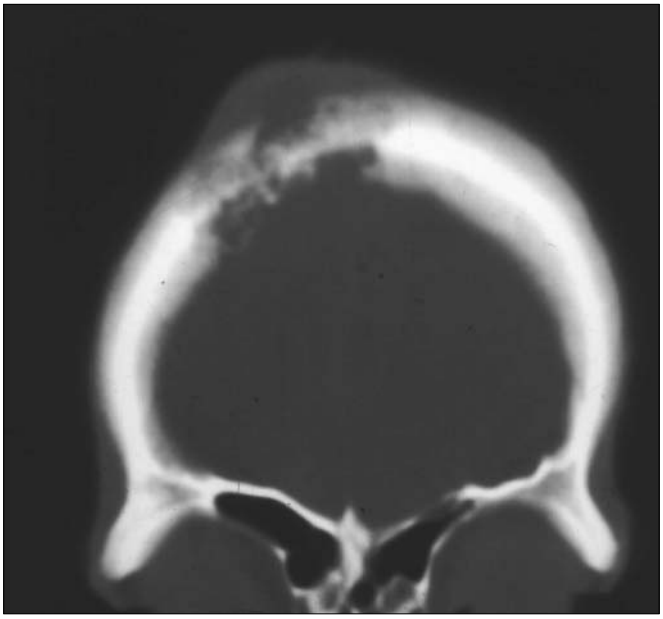

Fig. 4: Case 4. CT scan shows soft-tissue swelling of the scalp adjacent to the area of osteomyelitis of the skull and inflammation of the meninges in the same region.

presive therapy, malignancy, malnutrition and diabetes may be underlying factors.

The symptoms of miliary TB are fever, weight loss and weakness.[25] Dyspnea suggests that the miliary lesion is causing hypoxemia. Findings of tachycardia, tachypnea, high temperature and splenomegaly are common. Choroid tubercles, small white lesions representing granulomata of the retina, are infrequent. The findings on chest radiography, diffuse nodules of less than 2 mm diameter, are pathognomonic (Fig. 4). The mean age of patients with miliary TB studied retrospectively in Edinburgh over 2 periods was 59 years in the 1960s and 73 years in the late 1980s.[26] The mortality rate rose from 25% during the first period to 50% in the second. In 40% of the patients, the results of chest radiography were reported as normal,[26] but miliary lesions are often missed.[27] Miliary TB may lead to adult respiratory distress syndrome.[28] Hyponatremia is present in 10% of cases[25] and may be due to inappropriate antidiuretic hormone secretion. Anemia occurs in two-thirds of cases of miliary TB and is usually the normochromic, normocytic form. Leukopenia may occur as a result of bone marrow infiltration with granulomata, but this is rare. Elevation of alkaline phosphatase level is not uncommon and usually reflects periportal granulomatous inflammation. The negative tuberculin skin test encountered in as many as 50% of cases of miliary TB should not dissuade the physician from making the diagnosis.[25] When miliary TB is suspected and sputum examination does not reveal acid-fast bacilli, bone marrow or liver biopsy may lead to the correct diagnosis.[29] Recent, positive blood culture results for mycobacteria have been reported as increasingly common in BACTEC nonradiometric systems (Becton-Dickinson Instruments Systems, Maryland) in patients with AIDS.[30]

TB of the central nervous system

TB meningitis is the most common form of TB of the central nervous system, but solitary or multiple brain lesions, lesions of the spinal cord and even involvement of the ears and eyes have been reported.[12] Classical tuberculous meningitis differs from acute bacterial meningitis in that it has a slower, more insidious onset. However, the symptoms are similar and include fever, anorexia, malaise, nausea, vomiting, headache and mental obtundation. The clinical symptoms have been described as presenting in 3 stages. Stage 1 has no neurologic signs, but there are symptoms of headache and fever. Stage 2 has focal neurologic abnormalities. People in stage 3, with coma, have the highest rates of mortality and neurologic sequelae.[31]

The pathogenesis of TB meningitis begins with the hematogenous seeding of the brain in a site adjacent to the meninges, which then ruptures into the subarachnoid space to produce meningitis. Only a small number of organisms are necessary to provoke the tissue reaction. A gelatinous exudate may collect at the base of the brain, interfering with cranial nerve function and provoking hydrocephaly. A vasculitic process is most commonly seen at the base of the brain and may cause infarction and neurologic sequelae.

Diagnosis of tuberculous meningitis depends on a high index of suspicion, especially in children, and recent contact with a case of TB. In cases of TB meningitis, the cerebrospinal fluid initially shows leukocytosis, but over a period of days, the predominant cell is the lymphocyte. The protein level is elevated and the glucose level decreased. The cerebrospinal fluid is seldom positive on direct smear examination for acid-fast bacilli (in only 25% of cases),[31] but the proteinaceous pellicle may capture organisms and should be removed from standing cerebrospinal fluid and stained. It may take 10 days to 8 weeks for positive culture results to appear. Therefore, antituberculous drug treatment should be started immediately, while awaiting the results. Any delay in the institution of treatment increases the risk of progressive neurologic sequelae.[31] TB meningitis is a clear indication for steroids, recommended for 6 to 12 weeks, beginning with a high dose and tapering gradually.[32-34]

Case 5: Abdominal TB

A 45-year-old man with biopsy-proven dermatomyositis continued to report fever and weight loss, despite increasing doses of corticosteroids. On the evening of admission, he was experiencing severe abdominal pain. In the emergency department, he was in acute distress, with a temperature of 40°C, heart rate of 120 beats/min and blood pressure of 140/80 mm Hg. On examination of the abdomen, there was guarding and absence of bowel sounds. The abdominal film showed air under the diaphragm. At surgery, the terminal ileum was perforated, and a 6-cm section was resected (Fig. 5). After the surgery, management in the intensive care unit was required because of persistent shortness of breath. Review of the chest radiograph demonstrated a right upper lobe cavitary lesion. Sputum specimens were smear positive for acid-fast bacilli. A review of the pathologic material resected at surgery showed multiple granulomas throughout the bowel wall and acid-fast bacilli in all layers (Fig. 6).

This man's pulmonary and bowel TB resolved with administration of 4 antituberculous drugs in the first 2 months and 2 drugs over the next 4 months. His dermatomyositis was easily controlled with low-dose corticosteroids after recovery from the TB.

TB peritonitis is difficult to diagnose. The symptoms are those of abdominal distension, low-grade systemic fever and weight loss. Peritoneal aspiration is associated with a risk of rupture of matted bowel and is seldom diagnostic, but laparoscopic biopsy is diagnostic in 77% of cases.[35]

Other sites

TB may reactivate at any site of hematogenous dissemination. Tuberculous pericarditis and TB of the eye, ear, skin or soft tissue are infrequent. However, appropriate specimens should be obtained for culture and pathologic examination in cases of chronic infection in people at high risk.

TB pericarditis deserves special mention because of the potential for the life-threatening complication of cardiac tamponade. Pericardiocentesis may be not only diagnostic

but therapeutic. As in TB meningitis, there is a clear indication for corticosteroids in addition to antituberculous treatment in this case to prevent pericardial constriction.[36]

Conclusion

The cases outlined here serve to remind us that although TB is a systemic disease transmitted by droplet spray from the cough of a person with infectious pulmonary TB, it may spread hematogenously to any organ system. The classic presentation of cough, fever and weight loss is less predictably present in those at extremes of age and with underlying immunosuppressive disease. The diagnosis depends on a physician considering the possibility of TB and obtaining appropriate specimens for culture. Fluid is less likely than tissue to be diagnostic because of the dilution factor. The fluid, whether from the pleural cavity, the abdominal cavity, lumbar puncture, joint aspiration or pericardial aspiration, may initially have a predominance of polymorphonuclear leukocytes, but within 2 weeks, lymphocytes predominate. The protein level is elevated and glucose diminished. Newer tools for diagnosis increase the speed of obtaining culture results, but the PCR, although rapid, is only reliable if enough organisms are present to yield a positive smear. PCR may yield false-positive results and is licensed for use only with sputum.

Although the rates of TB in Canada have plateaued in the past decade, the contribution of extrapulmonary TB has risen from 20% to 25%. Treatment of TB is curative regardless of site, if it is instituted early and if the organism remains sensitive to all first-line antituberculous drugs; however, the outcome depends on compliance with prescribed drug regimens. Case finding of extrapulmonary TB depends on an alert pratitioner considering its possibility in high-risk populations.

I would like to acknowledge the provincial and territorial tuberculosis directors and their teams for their contribution to the Canadian Tuberculosis Reporting System, and specifically the help of Penny Nault with analysis of rates of extrapulmonary site for aboriginal and foreign-born people.

Competing interests: None declared.

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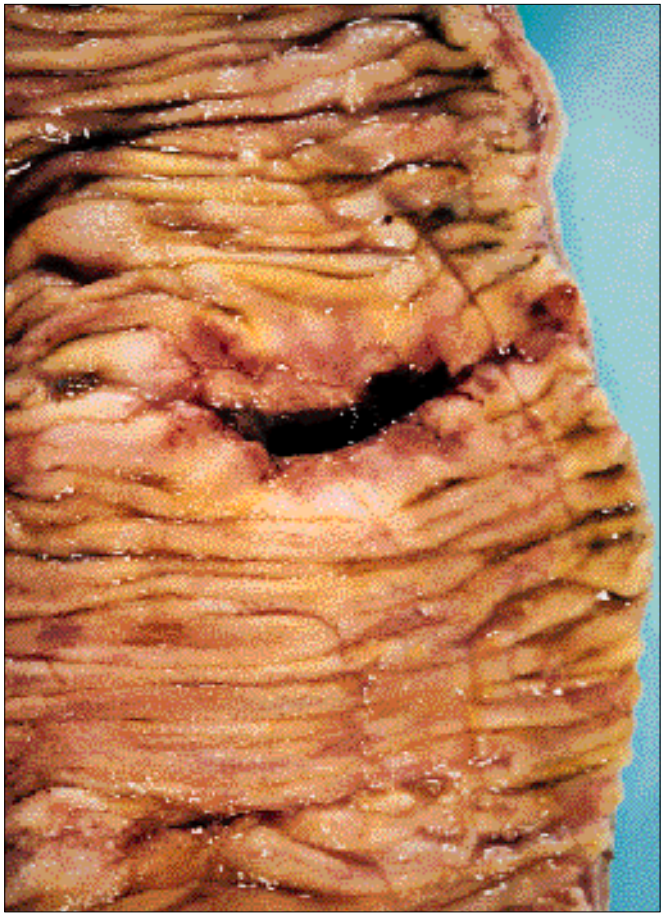

Fig. 5: Case 5. Resection of the terminal ileum at the location of the performation, secondary to the granulomatous process which involved all layers of the bowel.

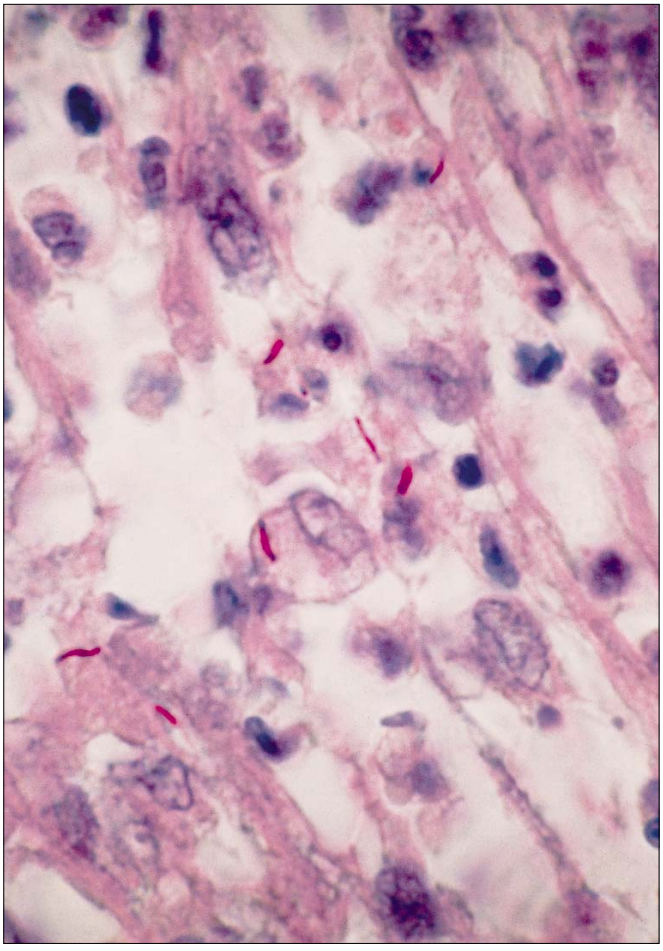

Fig. 6: Case 5. Oil immersion microscopy of the granulomatous inflammation shows many acid-fast bacilli.

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