

Hepatic abscess complicating ulceroglandular tularemia

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In a patient with the clinical features of classic ulceroglandular tularemia a solitary hepatic abscess was found during an ultrasound examination. Hepatic tularemia has rarely been reported since the advent of specific therapy, which prevents the disease from reaching the disseminated state. This case, however, shows that the liver can be involved early in the course of tularemia. Increased serum levels of hepatic enzymes may be the only sign of such a complication.

Chez un patient qui montrait les caractéristiques cliniques de la tularémie ulcéro-ganglionnaire classique un abcès hépatique solitaire fut découvert à l'échographie. La tularémie hépatique a rarement été signalée depuis l'avènement d'un traitement spécifique, qui empêche la maladie de se disséminer. Ce cas montre, toutefois, que le foie peut être touché tôt dans l'évolution de la tularémie. L'augmentation des taux sériques des enzymes hépatiques peut être la seule manifestation de cette complication.

Since 1928, when Francis¹ proposed a system of classification for tularemia, many reports have described epidemics and sporadic cases involving the five classic forms: glandular, ulceroglandular, typhoidal, oculoglandular and oropharyngeal. In addition to the relatively common pleuropulmonary complications, many unusual presentations have also been described: meningitis,² pericarditis,³ peritonitis,⁴ osteomyeli-

tis and rashes.⁵ Hepatic tularemia was once seen at the autopsies of patients whose disease had become disseminated because they could not be treated,^{1,6,7} but it has rarely been reported since the advent of chemotherapy. We describe a patient with classic ulceroglandular tularemia in whom there was focal necrotizing hepatitis with the formation of a central abscess early in the course of the infection. *Francisella tularensis* was documented by needle aspiration and culture of liver tissue. To our knowledge, identification of the organism from an isolated hepatic abscess along with successful treatment with chemotherapy alone has not previously been reported.

Case report

In a previously healthy 66-year-old man a spiking fever developed abruptly, with chills, myalgia, progressive weakness and anorexia. Later that week he complained of mild discomfort in the right axilla and a severe, continuous headache with photophobia. A local physician prescribed a 5-day course of ampicillin to be taken orally, but there was no improvement. The patient was then admitted to our hospital, where it was learned that he had been on a hunting trip before the onset of his illness. He remembered having cut his right thumb while cleaning a wild rabbit and some partridges.

The patient showed signs of toxemia only during recurring bouts of fever (temperature up to 40°C measured orally) but otherwise appeared comfortable. An indolent ulcer was noted on the right thumb and a mobile, nontender lymph node 2 × 3 cm in size was palpated in the right axilla. There was no conjunctivitis,

pharyngitis or hepatosplenomegaly.

The leukocyte count and hematocrit were normal, but the erythrocyte sedimentation rate (determined by the Westergren technique) was 87 (normally 0 to 6.5) mm/h. The following serum levels were determined: glutamic oxaloacetic transaminase 59 (normally 7 to 27) U/l, glutamic pyruvic transaminase 81 (normally 4 to 36) U/l, γ -glutamyl transpeptidase 169 (normally 11 to 63) U/l, alkaline phosphatase 194 (normally 36 to 92) U/l and bilirubin normal.

The chest x-ray film was normal. An abdominal ultrasound examination showed a hypoechoic area 2 cm in diameter near the anterior surface of the right lobe of the liver; this could not be visualized on technetium 99m and gallium scintigraphic scans of the same area (Fig. 1). On the 4th day in hospital an aspiration biopsy of the hypoechoic part of the liver, performed under ultrasound guidance, yielded dense, viscous pus between fragments of macroscopically normal liver tissue. Microscopic examination revealed necrotic foci edged by granulation tissue that contained many polymorphonuclear cells; the surrounding liver parenchyma showed nonspecific reactive inflammation (Fig. 2).

The hepatic specimen was plated directly on glucose-cystine agar (Difco Laboratories, Detroit) and on chocolate agar supplemented with 1% IsoVitalex (Baltimore Biological Laboratories, Cockeysville, Maryland). After 48 hours of incubation colonies of small gram-negative coccobacilli appeared only on the chocolate agar. The Laboratoire de santé publique du Québec identified these as *F. tularensis*. Repeated attempts to isolate the same organism from

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blood samples and the skin lesion were unsuccessful.

Following a 10-day course of streptomycin, 500 mg given intramuscularly every 12 hours, the patient recovered uneventfully. An ultrasound scan of the liver was then normal. The titre of agglutinating serum antibodies against *F. tularensis* rose from zero on the 10th day after the onset of his illness to 1:640 on the 26th day. Tests for *Brucella* agglutinins gave negative results.

Discussion

This case clearly illustrates that hepatic involvement can occur early in the evolution of ulceroglandular tularemia rather than only in the terminal stage.^{1,6,7} The early detection here reflects the improvement in diagnostic capabilities, including liver biopsy. The abdominal ultrasound examination in our case was done solely because we had found elevated serum levels of hepatic enzymes. Recently Martone and associates⁸ reported hepatomegaly in two of three cases of pulmonary tularemia; the results of liver function tests were abnormal in all three.

These observations suggest that dissemination to the liver in tularemia may be more frequent than has been recognized.

The pathological findings in our case were consistent with hepatic tularemia.^{1,6} Although tularemia is usually considered in the differential diagnosis of hepatic granulomas, the most frequent pathological findings in the liver of a patient with tularemia are not granulomas but necrotic foci surrounded by neutrophil infiltration,⁹ as in our case. However, typical granulomas may still be observed in tularemia, especially in the lymph nodes early in the course of infection.¹⁰ The good clinical response to chemotherapy alone in our case may have been due to the absence of fibrotic encapsulation and the small size of the abscess. Others have recently reported the efficacy of antimicrobial therapy combined with percutaneous drainage of liver abscesses.^{11,12}

The probable, though unproven, mode of dissemination in our case was bacteremic spread from the digital ulcer to the liver. Standard blood cultures yielded no organisms, but special techniques, such as di-

rect spreading of the patient's blood on glucose-cystine agar or supplemented chocolate agar,¹³ were not done. We easily recovered the organism from the hepatic specimen by directly plating it on supplemented chocolate agar, but no growth occurred on the classic glucose-cystine agar medium. The use of simpler media, like chocolate agar, has already been suggested.¹⁴ However, our glucose-cystine agar plates were not tested with a nonvirulent control strain of *F. tularensis* before their use. This alone could explain why the isolate did not grow on this medium.

Tularemia is endemic in western and central Canada, and a recent epidemic occurred in Quebec.¹⁵ Physicians should bear in mind the possibility of liver involvement when evaluating a patient suspected of having tularemia. Elevated serum levels of hepatic enzymes may be the only sign of this complication and should prompt an ultrasound examination of the liver. Although nonspecific, this procedure could guide further investigation. In attempts to culture *F. tularensis* we recommend the use of enriched

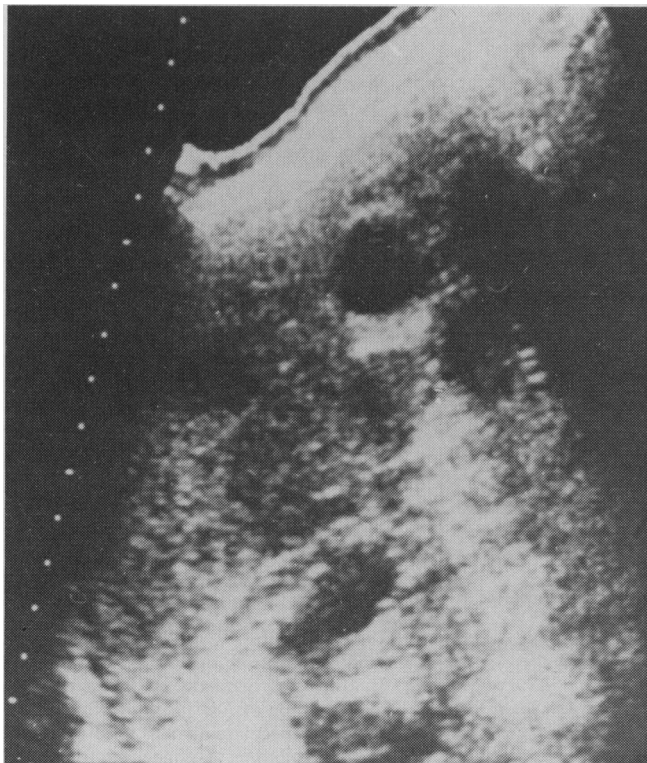


FIG. 1—Transverse ultrasound scan of portion of right lobe of liver. Hypoechoic mass 2 cm below skin shows fluid characteristics and some cellular elements; it is consistent with an abscess.



FIG. 2—Wall of abscess with some steatosis and nonspecific reactive inflammation of liver tissue in lower right (hematoxylin-eosin and saffron; $\times 250$).

Intermediate Prescribing Information

Lopresor® (metoprolol tartrate)

50 mg and 100 mg tablets
200 mg slow-release tablets

Therapeutic Classification

Antihypertensive and anti-anginal agent.

Actions

Metoprolol tartrate is a beta-adrenergic-receptor-blocking agent with predominant blocking effect on beta₁ receptors.

Indications

a) Mild and Moderate Hypertension:

Usually used in combination with other drugs, particularly a thiazide diuretic, however, may be tried alone as an initial agent in those patients whose treatment should be started with a beta-blocker rather than a diuretic. The combination of Lopresor with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than Lopresor alone. Incompatibility with other antihypertensive agents has not been found, experience is limited however. Not recommended for the emergency treatment of hypertensive crises.

b) Angina Pectoris

Lopresor is indicated in patients with angina pectoris due to ischemic heart disease.

Contraindications

Sinus bradycardia, second and third degree A-V block, right ventricular failure secondary to pulmonary hypertension, congestive heart failure, cardiogenic shock, anesthesia with agents that produce myocardial depression, e.g. ether and chloroform.

Warnings

Cardiac Failure: Special caution should be exercised when administering Lopresor to patients with a history of heart failure, since inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients without a history of cardiac failure, continued depression of the myocardium can lead to cardiac failure. At the first sign of impending cardiac failure, patients should be digitalised and/or given a diuretic and observed closely.

Lopresor does not abolish the inotropic action of digitalis on the heart muscle, however, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of Lopresor when the two drugs are used concomitantly. The effects of beta-blockers and digitalis are additive in depressing A-V conduction. If cardiac failure continues, despite adequate digitalisation and diuretic therapy, discontinue Lopresor therapy.

Abrupt Cessation of Therapy with Lopresor: Warn patients against abrupt discontinuation. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias in patients with angina following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris.

When discontinuation of Lopresor is planned in patients with angina, dosage should be gradually reduced over a period of about two weeks and the patient carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, Lopresor should be discontinued stepwise, under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with Lopresor be reinstated promptly, at least temporarily.

Various skin rashes and conjunctival xerosis have been reported. A severe syndrome (oculo-muco-cutaneous syndrome) whose signs include conjunctivitis sicca and psoriasisiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic-blocking agent (propranolol) but has not been observed with Lopresor or any other such agent. Physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Severe sinus bradycardia may occur, in such cases, dosage should be reduced.

Lopresor may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of Lopresor may be followed by an exacerbation of the symptoms of hyperthyroidism including thyroid storm.

Precautions

Careful monitoring of patients with diseases associated with bronchospasm is mandatory and a bronchodilator must be administered concomitantly.

Administer with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia.

Adjust dosage individually when used concomitantly with other anti-hypertensive agents.

Closely monitor patients also receiving catecholamine-depleting drugs, such as reserpine or guanethidine. Lopresor should not be combined with other beta-blockers.

Appropriate laboratory tests should be performed at regular intervals during long-term treatment.

Lopresor should not be given to patients receiving verapamil. In exceptional cases, when in the opinion of the physician concomitant use is considered essential, such use should be instituted gradually, in a hospital setting, under careful supervision.

In patients undergoing elective or emergency surgery: Lopresor should be withdrawn or gradually following recommendation given under Abrupt Cessation of Therapy (see WARNINGS). Available evidence suggests that the clinical and pharmacological effects of beta-

blockade induced by Lopresor are no longer present 48 hours after cessation of therapy.

In emergency surgery, effects of Lopresor may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levaterenol.

Usage in pregnancy and nursing mothers: Lopresor crosses the placental barrier and appears in breast milk. It should not be given to pregnant women as it has not been studied in human pregnancy. If use of the drug is deemed essential in nursing mothers, the patient should stop nursing.

Usage in children: There is no experience with Lopresor in the pediatric age groups.

Adverse reactions

Cardiovascular: Congestive heart failure (see WARNINGS), secondary effects of decreased cardiac output which include: syncope, vertigo, lightheadedness and postural hypotension; severe bradycardia, lengthening of PR interval, second and third degree A-V block, sinus arrest, palpitations, chest pains, cold extremities, Raynaud's phenomenon, claudication, hot flushes.

Central Nervous System: headache, dizziness, insomnia, mental depression, lightheadedness, anxiety, tinnitus, weakness, sedation, vivid dreams, vertigo, paraesthesia. **Gastrointestinal:** diarrhea, constipation, flatulence, heartburn, nausea and vomiting, abdominal pain, dryness of mouth.

Respiratory: shortness of breath, wheezing, bronchospasm, status asthmaticus.

Allergic/Dermatological (see WARNINGS): exanthema, sweating, pruritus, psoriasisiform rash. **EENT:** blurred vision and non-specific visual disturbances, itching eyes.

Miscellaneous: tiredness, weight gain, decrease in libido. **Clinical Laboratory:** The following laboratory parameters have been rarely elevated: transaminases, BUN, alkaline phosphatase and bilirubin. Thrombocytopenia and leucopenia have been reported rarely.

Symptoms and Treatment of Overdosage

Symptoms: bradycardia, congestive heart failure, hypotension, bronchospasm, hypoglycemia.

Treatment: Discontinue Lopresor and observe patient closely. In addition, if required, the following therapeutic measures are suggested.

1. **Bradycardia, and hypotension:** Initially 1-2 mg of atropine sulfate should be given intravenously. If a satisfactory effect is not achieved, a pressor agent such as norepinephrine may be administered after preceding treatment with atropine.

2. **Heart Block: (second or third degree)** Isoproterenol or transvenous cardiac pacemaker.

3. **Congestive heart failure:** Conventional therapy.

4. **Bronchospasm:** Aminophylline or a beta₂-agonist.

5. **Hypoglycemia:** Intravenous glucose.

Large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of Lopresor.

However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

Doasage and Administration

a) Hypertension: Initial Dose: 50 mg b.i.d. If adequate response is not seen after one week, dosage should be increased to 100 mg b.i.d. In some cases the daily dosage may need to be increased by further 100 mg increments at intervals of not less than two weeks up to a maximum of 200 mg b.i.d., which should not be exceeded.

Usual Maintenance Dose: 150-300 mg daily. When combined with another antihypertensive agent which is already being administered, Lopresor should be added initially at a dose of 50 mg b.i.d. After 1 or 2 weeks the daily dosage may be increased if required, in increments of 100 mg, at intervals of not less than 2 weeks, until adequate blood pressure control is obtained.

b) Angina pectoris: Initial Dosage: 50 mg b.i.d. for the first week. If response is not adequate, the daily dosage should be increased by 100 mg for the next week. The need for further increases should be closely monitored at weekly intervals and the dosage increased in 100 mg increments to a maximum of 400 mg/day in 2 or 3 divided doses.

Usual Maintenance Dosage: 200 mg/day. **Dosage Range:** 100-400 mg per day in divided doses. A dose of 400 mg/day should not be exceeded.

c) Slow-release Lopresor SR 200 mg: Lopresor SR 200 mg is intended only for maintenance dosing in those patients requiring doses of 200 mg per day.

Treatment must always be initiated and individual titration of dosage carried out using the regular tablets. Patients with hypertension or angina pectoris on a maintenance regimen of one 100 mg tablet twice daily may be changed to one Lopresor SR 200 mg tablet taken in the morning.

Lopresor SR 200 mg tablets should be swallowed whole.

Availability

Lopresor
Tablet: 50 mg: Film coated, light red, capsule-shaped tablet, embossed 51 and scored on one side and GEIGY on the other.

Tablet: 100 mg: Film coated, light blue, capsule-shaped tablet, embossed 71 and scored on one side and GEIGY on the other. Bottles of 100 and 500 tablets.

Lopresor SR 200
Slow-release Tablet: 200 mg: Film-coated, light yellow, round tablet, embossed GEIGY on one side and CDC on the other. Bottles of 100 tablets.

Product monograph supplied on request.

Geigy

Mississauga, Ontario
LSN 2WS
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chocolate agar, as well as the standard glucose-cystine agar.

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