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Toxic epidermal necrolysis (TEN) and development of liver abscesses

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Abstract

Pharmacologic hypersensitivities commonly express cutaneous manifestations, and the highest mortality is found in Stevens Johnson's syndrome and toxic epidermal necrolysis, mostly associated with antibiotics and anticonvulsive drugs. Toxic epidermal necrolysis is related in 80% of cases to pharmacologic hypersensitivity and systemic consequences may be found; hepatic injury has been described, but the finding of liver abscesses has not been reported among common injuries. The case of a patient with a rapid development of multiple liver abscesses in the clinical setting of hypersensitivity due to lamotrigine and the discussion of probable etiologies and management is presented. (Gac Med Mex. 2015;151:479-84)

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KEY WORDS: *Toxic epidermal necrolysis. Drug hypersensitivity. Liver abscess. Intravenous immunoglobulin.*

Introduction

Toxic epidermal necrolysis (TEN), also referred to as Lyell's syndrome, is a severe pharmacodermia with a low incidence (approximately 2 cases per million), but high mortality. It occurs at all ages, in all races and in both genders[1]. Approximately 80% of the TEN cases are induced by drugs, but other etiologies have been proposed, such as *Mycoplasma* and *Klebsiella* spp infections, neoplasms and graft versus host reactions[2]. Th drugs with the highest risk for the development of TEN are: sulphonamides, aminopenicillins, quinolones, cephalosporins, acetaminophen, carbamazepine, lamotrigine, phenobarbital, phenytoin, oxicam, non-steroid antiinflammatory drugs, allopurinol and corticosteroids[3].

On the other hand, liver abscesses have an incidence of 0.5-0.8% in the general population[4]. In the USA, annual hospitalization incidence for pyogenic liver abscess is 3.59 per each 100,000 inhabitants, with higher incidence among males; the risk increases with age, and the group at the highest risk is that of 65-84 years of age. Mortality in hospitalized patients due to pyogenous hepatic abscess was 5.6%, with an incidence of 0.17-0.24 per each 100,000 inhabitants. The factors that have been associated with higher mortality are: age older than 65 years, sepsis, comorbidities such as cirrhosis, chronic kidney disease and cancer[5].

With regard to the etiology, pyogenous abscesses account for three quarters of liver abscesses in developed countries. However, amebic hepatic abscesses are the most common cause worldwide. Most patients with pyogenous liver abscess have polymicrobial infection

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and aerobic and anaerobic gram-negative microorganisms are usually isolated. Most microorganisms originate in the gut and the most common germs are: *Escherichia coli, Klebsiella pneumoniae,* bacteroids, enterococci, anaerobics and some microaerophilic streptococci. Some species of staphylococci, hemolytic streptococci and *Streptococcus milleri* are usually present if primary infection is bacterial endocarditis or sepsis of dental focus. In immunocompromised patients, such as AIDS patients, patients on treatment with chemotherapy or post-transplanted patients, the risk for abscess by fungi and opportunistic microorganisms is increased[6].

In the following sections, the case of a female patient with no predisposing factors who experienced a drug hypersensitivity reaction to lamotrigine with subsequent accelerated development of multiple liver abscesses is reviewed.

Case presentation

This is the case of a 55-year old female patient with a history that included systemic arterial hypertension diagnosed 5 years before and managed with enalapril and depressive syndrome of unspecified evolution, managed with bromazepam, with recent addition of lamotrigine.

The patient's ailment had started one week prior to her admission with odynophagia and non-quantified fever, which were managed with ampicillin and diclofenac. Three days later, she noticed the presence of welt-like lesions on the limbs and abdomen, with progressive dissemination. Asthenia, adynamia, fever and blisters on the soles of her feet added up to her symptoms, and for this reason she decided to go to the Emergency Department, where she was admitted with stable vital signs, a temperature of 38 °C, tender vesicular lesions containing a serous fluid with predominance on the metatarsal region of the soles of the feet, with a diameter larger than 6 cm, and erythematous lesions on the anterior side of the thorax, forehead and forearms with formation of serous vesicles smaller than 5 mm, with burning sensation to the touch and referred to as newly appearing, in addition to purulent discharge from both conjunctives and conjunctival erythema, erythematous pharynx and grade II tonsillar hypertrophy, with no further abnormalities on physical examination. Paraclinical data at admission were the following: WBC: 10,000/mm^3; hemoglobin: 12.7 g/dl; hematocrit: 38%; MCV: 92.5 fl; MCH: 30.9 pg; PLT: 169,000/mm^3; glucose: 155 mg/dl; urea: 23.5 mg/dl; BUN: 11 mg/dl; Cr: 0.6 mg/dl; Na: 131 mmol/l; K: 3.6 mmol/l; Cl: 96 mmol/l; total bilirubin: 2.2 mg/dl; indirect bilirubin: 2.2 mg/dl; total protein: 6.3 g/dl, albumin: 2.9 g/dl; AST: 617 U/l; ALT: 1141 U/l; PA: 323 IU/l; GGT: 522 U/l; arterial blood gas pH: 7.45; PCO_2: 24.2 mmHg; PO_2: 64.1 mmHg; SO_2%: 94.4; FIO_2: 21%; HCO_3: 16.6; base(Ecf): -6.6 mmol/l and PO_2/FiO_2: 305 mmHg. Due to altered trasaminases, liver and biliary tract ultrasound was performed, with the following results: liver with preserved echogenicity with intra- and extrahepatic biliary tract without dilation, with 9-mm porta, 4-mm ductus choledochus, gallbladder with dimensions of 76 x 34 mm, with 2-mm wall; no sludge or calculi were appreciated; pancreas with preserved echogenicity, and both kidneys with no alterations. The patient was admitted into Internal Medicine with a diagnosis of pharmacodermia, conjunctivitis and bacterial pharyngotonsillitis. Management was started with methylprednisolone, ranitidine, sodium metamizole, acetaminophen, chloramphenicol (eye drops) and levofloxacin, without improvement of the lesions. During the following two days, the patient evolved with disseminated phlyctenae, positive Nikolsky sign in the eyelids, forehead, neck, shoulders and ankles and painful exudative erosions predominantly on the posterior thorax and lower limbs. A biopsy was obtained of the thigh skin with active vesicular involvement (Fig. 1). The decision was made to admit the patient in the Intensive Care Unit with the diagnosis of TEN, with a calculated body

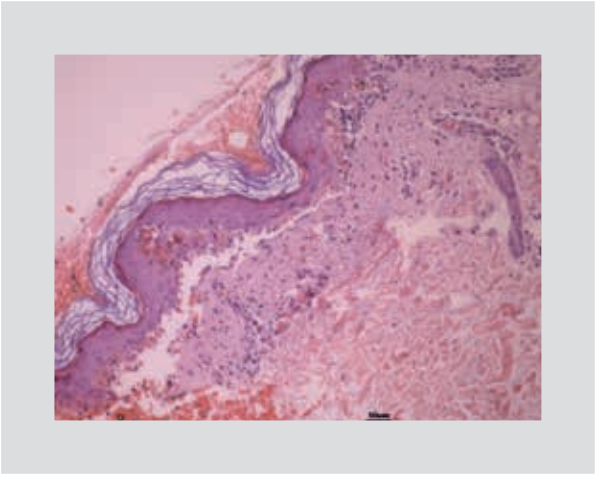

Figure 1. *Right tigh biopsy. A fragment of skin is observed where the corneal layer of epidermis shows extensive, increased keratinization with a "basket weave" pattern (orthokeratosis). At the prickle cell layer there are several keratinocytes undergoing apoptosis (Civatte bodies). The basal layer has necrotic cells and some exhibit vacuolization of their cytoplasm, with papillary dermis detachment, abundant material with necrotic appearance, blood vessels with lymphocytic inflammatory infiltrate and score plasma cells. (Credits: Dr. Citlali Pasillas Bravo, Dr. Erick Abraham Contreras López, Dr. Nayeli Belem Gabiño López. Pathologists at H&E Diagnóstico).*

surface area affected of 40%, SCORTEN of 4 points at admission and calculated mortality of 58%. Management with intravenous immunoglobulin was started at a dose of 1 g/kg/day for 3 days for a total dose of 3 g/kg. Dermal lesions were reduced and there was symptom improvement; the patient referred abdominal dystension and the second day of treatment she had leukopenia with moderate neutropenia.

At the fourth day of stay she presented a systemic inflammatory response with fever higher than 38 °C, leukocyte increase, non-productive cough, pain in the right hypochondrium and early post-prandial fullness sensation. Chest x-ray revealed right hemidiaphragm elevation with no evidence of consolidation, and the abdominal USG with liver scan showed rounded, heterogeneous images, with well defined edges, no vascularity at color Doppler application; the largest had 67 x 61 mm dimensions, the smallest, 38 x 26 mm, and were located mainly in the right liver lobe, with the largest adjacent to the portal vein. Subsequently, a contrasted thoracoabdominal tomography was performed, which reported multiple rounded, hypodense images in the hepatic gland, the largest of 3.5 x 4.5 cm size, and consistent with multiple liver abscesses (Fig. 2).

Antibiotic therapy was started with meropenem, metronidazole and vancomycin for 7 days, with the patient persisting with systemic inflammatory response, neutrophilic leukocytosis, fever and tachycardia; thus, a percutaneous drainage is performed, by means of which hematopurulent material is obtained; bacterial cultures are reported to be negative. The inflammatory response subsided with the percutaneous drainage and antibiotic continuation for 21 days. Since there was a general status improvement, signs and symptoms of inflammatory response subsided, the patient tolerated the oral route and liver function tests were improved, the decision was made to discharge her from the intensive care department.

The patient was admitted to the Internal Medicine hospitalization area, where she remained hemodynamically stable with no systemic inflammatory response relapse, but a hospital-acquired pneumonic focus was found; therefore, carbapenem was continued until the sputum culture result was obtained, and the patient was managed with ceftriaxone. Percutaneous liver drainage catheters were removed when no more than 10 cc/day output was obtained. The patient continued to improve and was discharged to her home. The study protocol was applied to serum tests in order to establish the etiology, with polymerase chain reaction (PCR) for positive *Entamoeba hystolitica.*

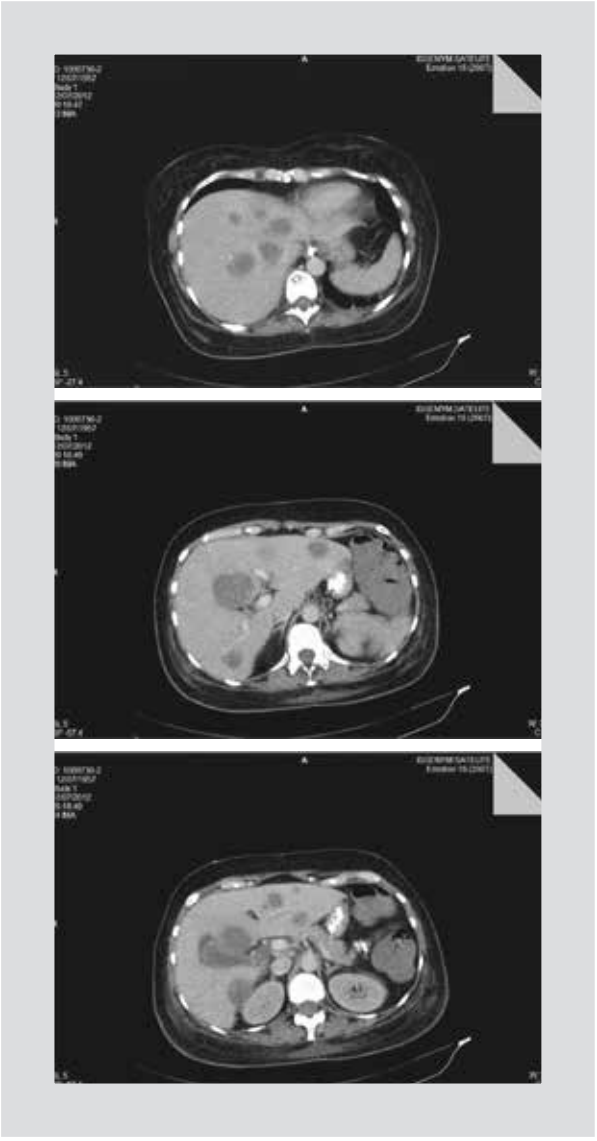

Figure 2. *Abdominal contrasted tomography. Rounded intrahepatic hypodense lesions can be appreciated in relation to multiple liver abscesses.*

Discussion

Lamotrigine is an anticonvulsant aromatic drug that acts by blocking the voltage-dependent sodium channels and produces a glutamate release inhibition. Its half-life is 25-30 h and it is metabolized in the liver, and its excretion occurs almost exclusively in urine as N-glucuronic. Its most common adverse effect is rash, which is more frequent at pediatric ages. High initial doses have been observed to represent a risk factor for the development of TEN[7].

As for the pathophysiological mechanisms of TEN, keratinocytes apoptosis is produced by granzyme products,

Table 1. SCORTEN scale for TEN severity

Variable	SCORTEN	Predicted mortality (%)
Age > 40 years	0-1 points	3.2
Malignancy	2 points	12.1
Tachycardia (> 120/min)		
Initial epidermal descamation surface > 10%	3 points	35.3
Urea nitrogen > 27 mg/dl	4 points	58.3
Serum glucose < 250 mg/dl		
Serum bicarbonate < 20 mEq/l	≥ 5 points	90

The presence of a variable parameter is evaluated as 1; absence is equivalent to 0. Total sum of all variables predicts the mortality risk. *(Adapted from Bastuli-Garin)*[6].

tumor necrosis factor alpha and the common pathway of caspases[8]. FAS ligands over-expression through these pathways induces apoptosis. This union can be selectively blocked with immunoglobulin G-type monoclonal antibodies[8,9].

Leukocytes are thought to be able to perpetuate apoptosis by FAS ligands, and an immune response is activated in parallel with an expansion of cytotoxic T CD8+ lymphocyte clones and the release of cytokines; interferon γ participation is also involved in the production of massive apoptosis of all epidermal layers[2,8]. Hydroelectrolytic disturbances and systemic infection can induce multiorgan failure, pulmonary thromboembolism and gastrointestinal hemorrhage. For this reason, TEN constitutes a therapeutic emergency at the moment of diagnosis[10].

Since initial symptoms are fever (usually higher than 39 °C), eye burning and dysphagia, and can precede cutaneous manifestations by 1-3 days, the diagnosis should be established promptly. Cutaneous lesions appear first in the trunk, and spread to the neck, the face, and proximal upper limbs, distal portions of the arms and the legs. Palms and soles can be spared or affected. The lesions start as erythematous macules and, subsequently necrosis appears and epidermal detachment that leave exudative erosions, also known as the Nikolsky sign[1,4]. Most patients have mucosal lesions, including painful oral and pharyngeal, ocular and genital erosions[3].

The extension of cutaneous involvement is one of the most important prognostic factors; hence, mild affection is said to involve epidermal detachment that can be mild (1-10% of total body surface area [TBSA]), mild (10-30% of TBSA) and serious (> 30% of TBSA)[1,3]. The SCORTEN is a disease severity scale with 7 parameters that include prognostic factors such as age and affected epithelial surface. A score of 5 or more is consistent with mortality higher than 90%[2] (Table 1).

Bad prognosis factors more commonly found are anemia and lymphocytopenia; the presence of neutropenia indicates a poor prognosis[3].

Definitive diagnosis is made with cutaneous biopsy; the histological analysis reports necrotic epidermis, at early stages, necrosis with intensively eosinophilic cells in the epidermis, limited mononuclear infiltrate into the dermis and, at late stages, extensive necrosis confluent to the entire epidermis. In addition, subepidermal blisters are observed, as well as an inflammatory infiltrate that, depending on its extension, is related to mortality: if the infiltrate is mild, mortality is 27%; if it is moderate, mortality is 53% and if it is severe, mortality is 71%[12]. Laboratory tests are non-specific to establish the diagnosis, but they are most helpful for prognosis[8,12].

The main differential diagnosis is Steven-Johnson, pustular erythema multiforme, linear immunoglobulin A dermatosis, paraneoplastic pemphigus, pustular pemphigus-like dermatosis, staphylococcal scalded skin syndrome and others such as acute graft versus host disease, acute generalized exanthematous pustulosis and Kawasaki's disease[8].

Primary treatment of TEN consists mainly in discontinuing the cause or triggering factor and proceed to management in a burn unit if necessary[1,2,10]. Multiple treatments have been proposed for these patients, such as corticosteroids, pentoxifylline, cyclophosphamide and cyclosporine. The use of corticosteroids has been associated with more morbidity due to infection, gastrointestinal tract bleeding and longer hospital stay. Cyclosporine has reported 0% mortality, but septic complications occur[2,13]. Prophylactic antibiotics are not recommended, since they increase mortality and bacterial resistance; they are reserved as treatment for cases of sepsis[1].

General measures include the following: isolation of the patient, warm environment to prevent hypothermia, venous access in non-involved skin for fluid balance control, enteral nutritional support because the patient is in a catabolic status and has higher metabolic requirements, bandages with petroleum jelly in affected areas and ensuring adequate pain management[14].

Therapeutics with drugs that block keratinocytes apoptosis offers great potential for the treatment of TEN[11]. Immunoglobulin is derived from a plasma pool

Table 2. Microorganisms causative of liver abscess

Source of infection	Common organism
Biliary	Gram-negative enteral microorganisms (enterococci)
Pelvic	*Bacteriodes fragilis*
Other intraperitoneal source	Aerobic/anaerobic mixed microorganisms (e.g., *B. fragilis)* Usually a single microorganism: staphylococci, streptococci (including *S. milleri)*
Hematogenous dissemination	*Candida* spp. Pyogenic: *K. pneumoniae* (Asia)
Immunocompromised	*Actinomyces* (rare)
Others	Amebic: *E. histolytica* (amebic abscess) Other parasites: *Ascaris lumbricoides*

Modified from de Heneghan, et al.[18].

of several thousands of donors and it is composed mainly of immunoglobulin G; it contains antibodies to FAS and for this reason it is able to block the Fas-FasL union, thus inhibiting apoptosis, and could be highly useful during early phases of the disease[11,15,16].

Administration of this drug is controversial. Authors in favor of this intervention base their opinion on descriptive studies or comparative studies with historical cohorts. One of the most relevant is the study conducted by Prins, et al. on 48 patients who received human immunoglobulin at a total average dose of 2.7 g/kg for a mean of 4 days, and it was associated with a rapid cease of mucosal detachment in 43 of all 48 patients (90%)[17].

Immunoglobulin side effects are moderate, and the most common is headache; other effects are: fever, rhinitis, myalgias, tachycardia, low back pain, abdominal pain, rash, nausea and vomiting[18]. Other very rare side effects that may occur are: hypotension, cytopenias, serum disease, disseminated intravascular coagulation (DIC), septic meningitis, alopecia, acute renal lesion, tubular necrosis, shock, myocardial infarction, deep venous thrombosis, syncope, adult respiratory distress syndrome (ARDS) and meningitis may appear in patients with a history of chronic headache. However, considering the seriousness of this disease and the low toxicity of intravenous immunoglobulin in comparison with steroids and other treatments, it is one of the best options currently available[19,20].

With regard to the presented case, the condition evolved with a prolonged fasting-associated immunosuppression state, with probable pathogenic proliferation and microbial translocation; signs and symptoms of infection at the dermal level were also found with dehydration and severe involvement of dermal barriers, which led to the subsequent appearance of multiple hepatic abscesses.

Within the etiology of liver abscesses, the most common cause is bacterial (Table 2); bacteria can infect the liver through 4 main routes: biliary, portal, arterial or by contact. Abscesses originating in the biliary system account for more than 40% and have the distinctive feature of being multiple and communicated with the biliary tract[21]. Abscesses originating in the portal system account for 15-20%, are secondary to sepsis of some abdominal organ that drains the portal system and may occur as complications of apendicitis, diverticulitis, Crohn's disease, perforated colon cancer, acute pancreatitis, etc.[6]. Abscesses originating in the arterial system account for 5-15%; the most frequent causes are: suppurative peripheral thrombophlebitis, endocarditis, and pulmonary, urinary, osteoarticular, otolaryngologic or stomatic infections (with the latter being less frequent). Abscesses by contact are infrequent and can be caused by pancreatitis or subphrenic abscesses, perforated ulcers or pyocholecysts.

This condition presents clinically with abdominal pain, oscillating fever (it is the most common symptom [77%]), nocturnal dyaphoresis, vomiting, anorexia, general malaise and weight loss. In elderly patients or with small lesions evolution can be insidious or hidden and they may present with symptoms of a primary infection (appendicitis, diverticulitis, etc.) prior to developing hepatic abscess symptoms. Conversely, when abscesses are multiple, the presentation can be more acute, as in the case of our patient, which occurred at the fourth day after admission. Some patients may present with cough or singultus due to diaphragmatic irritation. There is pain on palpation and percussion at the right upper quadrant; jaundice occurs at the last stage, unless there is suppurative cholangitis; some patients present with hepatomegaly and fever of unknown origin. Laboratory findings include leukocytosis (91%), normocytic normochromic anemia (64%) and high GSR. As a constant laboratory finding, an increase in CRP has been reported in 100% of cases, as well as an increase in alkaline phosphatase, hypoalbuminemia and serum transaminases in marginally abnormal ranges[4,6,21].

Table 3. Indications for hepatic abscesses drainage

- Not recommended: multiple small abscesses that respond to antibiotics (biliary duct obstruction should be excluded as a cause and, if needed, an endoscopic retrograde cholangiopancreatography with stent placement should be performed)
- Drainage with percutaneous aspiration: < 6 cm abscesses
- Drainage with percutaneous catheter: ≥ 6 cm abscesses
- Open surgery:
  - Percutaneous drainage failure
  - Large sized or multilobed abscesses
  - Associated intra-abdominal infection requiring surgical approach (e.g., cholelithiasis)

Modified from de Krige, et al.[19].

For the hepatic abscess diagnosis, ultrasound is preferred as the initial tool; it has 85-95% sensitivity and is able to identify lesions larger than 2 cm in diameter. Computed tomography (CT) has a sensitivity of 95% and is able to detect abscesses of down to 0.5 cm in diameter. The ultrasound describes hypoechogenic lesions with irregular margin; in the CT, they appear as low-density, poorly defined lobulated lesions[22].

Currently, the combination of antibiotic therapy and percutaneous drainage is the main form of treatment, and reduces mortality at rates ranging from 5 to 30%[23]. However, a small proportion of patients fail to respond adequately to minimally invasive treatment and require open surgical management.

Broad spectrum antibiotic therapy by the parenteral route should be based on the suspicion of an infectious focus for 2-3 weeks or until favorable clinical response is obtained. Subsequently, it should be complemented with oral antibiotic therapy for 2-4 weeks or until clinical, biochemical and radiological resolution of the abscess is demonstrated. Evidence suggests that antimicrobial therapy is usually not enough to resolve abscesses, even if they are smaller than 3 cm[22,24,25]. Finding an abscess smaller than 6 cm is recommended as a criterion to continue management only with antibiotic therapy, although other authors recommend drainage of any abscess larger than 3 cm[25]. Percutaneous drainage criteria are described in table 3.

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