

Exfoliation, Cholestasis, and Apparent Biliary Sepsis in a Woman with Adult-Onset Diabetes

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In consultation the authors were requested to evaluate a middle-aged diabetic woman for an apparent episode of biliary sepsis. The patient had been admitted to the dermatology service with a four-day history of rash and pruritus. This was initially thought to represent an allergic reaction to dicloxacillin in someone with a previous history of penicillin hypersensitivity. Persistent right upper quadrant pain, fevers, elevations of serum alkaline phosphatase, and a radionuclide scan which did not demonstrate a functioning gall bladder led to a cholecystectomy for acute cholecystitis and possible biliary sepsis. This diagnosis was not confirmed. Ultimately, this case illustrated the need to review carefully recent changes in any patient's drug regimen. Reactions to commonly prescribed agents may cause syndromes which are difficult to distinguish from episodes of apparent sepsis.

CASE PRESENTATION

A 52-year-old black woman with non-insulin dependent diabetes mellitus documented for over two years was admitted to the Dermatology Service at Yale-New Haven Hospital with a chief complaint of rash and pruritus of four days' duration.

She related the onset of her illness to shampooing with a mixture of Kwell and rug shampoo in an attempt to straighten her hair three weeks prior to admission. Since that time she had experienced fatigue, diminishing appetite, and intermittent cold sweats. Four days prior to admission, she noted pruritus in the left axilla associated with an erythematous rash. A physician prescribed a topical cream and lorazepam. The following day she visited a local hospital emergency room because of persistent rash and the onset of fever. Her temperature was noted to be 102° F. She was given a topical steroid cream and dicloxacillin despite a history of penicillin allergy. During the next two days the patient's fever persisted. The rash spread to involve both her trunk and extremities. She was referred to the Dermatology Service at Yale-New Haven Hospital and admitted for evaluation. Review of symptoms was otherwise unremarkable except for ill-defined right-sided abdominal discomfort which had been present for several weeks.

Her past medical history was remarkable for diabetes mellitus, controlled with oral hypoglycemic agents. She had been treated with acetohexamide (Dymelor); however, four weeks prior to admission her medication was changed to chlorpropamide

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(Diabinese). A known peptic ulcer had been inactive for several years. There was no prior history of atopy, asthma, eczema, psoriasis, or other skin disease. She had smoked one pack of cigarettes weekly for several years and had a past history of alcohol abuse.

The patient was aware of her allergy to penicillin. In the 1950s she received an intramuscular injection of penicillin after which she developed a generalized rash. There was no history of recent travel, nor were there any pets at home. Medications on admission included dicloxacillin, chlorpropamide, and a topical steroid cream.

The patient was described as well-developed, well-nourished, and in no acute distress, with a temperature of 102.2° F. Her skin was remarkable for generalized urticaria, with erythematous papules and plaques covering 60–70 percent of her body surface. Some plaque-like lesions contained pustules. There were numerous moist, weeping vesicles on erythematous bases found on the neck. Palms and soles were not involved. The nails, scalp, and mucous membranes were normal. She had no lymphadenopathy. Her abdomen was soft and non-tender without any appreciable organomegaly. Neurological examination was unremarkable.

Laboratory data on admission included a white blood count of 5,700 cells/ μ l with a differential count of 69 percent segmented neutrophils, 22 percent band forms, 5 percent lymphocytes, 2 percent monocytes, and 2 percent eosinophils. Her hematocrit was 41.5 percent and platelet count was 139,000/ μ l. Prothrombin time and partial thromboplastin time were within normal limits. Sedimentation rate (ESR) was 42 mm/hour (normal < 20). Serum chemistries included a serum sodium of 125 meq/L and bicarbonate of 17.5 meq/L. Blood urea nitrogen and serum creatinine were within normal limits, and her serum glucose was 423 mg %. Her urine specific gravity was 1.036 g/ml; urine pH was 5.0 with 2+ protein, 3+ glucose, moderate bile, and negative reactions for ketones and occult blood. Microscopic examination of her urine showed 0–1 white blood cells per hpf, and 0–1 red blood cells per hpf. Casts and bacteria were not seen. Arterial blood gases while the patient was breathing room air demonstrated a pH of 7.43, pO₂ of 105 mm Hg, pCO₂ of 27 mm Hg, and a bicarbonate of 17.2 meq/L. Chest X-ray showed plate-like atelectasis in the left lower lobe; no infiltrates were apparent. Except for sinus tachycardia at a rate of 100, her electrocardiogram was normal.

DR. ROBERT BALTIMORE (*Associate Professor of Pediatrics and Epidemiology, Yale University School of Medicine*): Were any pustular lesions unroofed, Gram-stained, and cultured?

DR. DONALD F. HEIMAN (*Postdoctoral Fellow in Infectious Diseases, Yale University School of Medicine*): Yes. Gram stains of the pustular skin lesions were done and no organisms were noted.

DR. BALTIMORE: In a patient such as this, presenting with fever and a vesiculo-pustular eruption, viral infection warrants serious consideration. This presentation is consistent with eczema herpeticum which occurs in patients with chronic eczema. Was there any past medical history or family history of eczema?

DR. HEIMAN: There was no family history of dermatologic disease obtained. Other than a rash at the time of penicillin administration 25 years ago, the patient had no prior history of skin diseases.

DR. GEORGE THORNTON (*Clinical Professor of Medicine, Chief of Medicine, Waterbury Hospital*): I am very concerned about the presence of bile in her urine, which

suggests that a more generalized disease process is occurring. Secondary syphilis certainly can involve both liver and skin and cause fever, as can sarcoidosis.

DR. HEIMAN: A serum VDRL test was nonreactive. She had no history of pulmonary, visual, or joint symptoms and her chest X-ray did not demonstrate any abnormalities consistent with sarcoidosis, but that diagnosis was considered. At the time of admission to the hospital the leading diagnosis was pustular drug eruption secondary to dicloxacillin in a patient with hypersensitivity to penicillin.

A PHYSICIAN: The patient actually had an axillary rash and fever prior to the time that dicloxacillin was prescribed. Is that not correct?

DR. HEIMAN: That is correct. At the time of admission, the patient's dicloxacillin and chlorpropamide were discontinued. She was treated with regular (crystalline zinc) insulin, fluid and electrolyte replacement. The topical steroids were continued. On the second hospital day, the patient remained febrile. Blood and urine cultures obtained on admission were reported negative. On the third hospital day, scleral icterus was noted. Total bilirubin was 7 mg/dl with a direct fraction of 4.48 mg/dl. Lactic dehydrogenase was 498 IU/L (normal 200–600). Serum glutamylxaloacetate transaminase was 31 IU/L (normal 15–35), alkaline phosphatase was 183 IU/L, (normal 10–70), and serum amylase was 53 IU/dl (normal 40–150).

A PHYSICIAN: What was happening to her white blood cell count and hematocrit? If hemolysis was also present, associated with fever and skin rash, angioimmunoblastic lymphadenopathy syndrome would be a consideration.

DR. HEIMAN: Her white blood cell count on the third hospital day was 10,500 cells/ μ l with a differential of 22 percent segmented neutrophils, 67 percent band forms, 7 percent lymphocytes, 2 percent monocytes, and 2 percent eosinophils. Her hematocrit, which was 41.5 percent on admission, dropped to the 35 percent range after hydration and remained stable at that level. A Coombs test was not performed.

DR. BALTIMORE: Was a skin biopsy done?

DR. HEIMAN: Yes, a skin biopsy was performed on the second hospital day. However, the results of that biopsy were not yet available. A medical consultant was concerned because of the presence of punch tenderness over the right upper quadrant in this febrile, jaundiced patient with diabetes. Both surgical consultation and HIDA ^{99m}Tc -labeled lidofenin scan were recommended. The working diagnosis was cholecystitis, with probable cholangitis. Vancomycin and gentamicin were administered to treat a potential hepatobiliary infection. Early on the fourth hospital day, a HIDA scan was performed. It showed no visualization of the gallbladder or bile ducts; however, radionuclide activity was detected in the small intestine. The scan was thought to be compatible with acute cholecystitis without evidence of common bile duct obstruction. An ultrasound examination of the abdomen demonstrated a small, thick-walled gall bladder. There was slight dilatation of the intrahepatic ducts. The diameter of the common bile duct was measured at the upper limits of normal. The ultrasound examination was thought to suggest cholecystitis. Kidneys, spleen, and pancreas were normal. How would you proceed at this juncture?

DR. MARY JEAN AHERN (*Assistant Clinical Professor of Medicine, Yale University School of Medicine*): How ill did the patient look?

DR. HEIMAN: She appeared quite toxic with fevers to 104° F. She complained only of mild discomfort in her right upper quadrant without radiation to her back or shoulders.

DR. AHERN: I would certainly begin antibiotics because an infectious hepatobiliary process is possible. I am not sure I would rush her to the operating room. The onset of her illness suggests a disease other than acute cholecystitis.

DR. JOHN MELLORS (*Assistant Professor of Medicine, Yale University School of Medicine*): The dermatologists' admitting diagnosis was a pustular drug eruption. At the time of admission she had been taking dicloxacillin and chlorpropamide. All of the patient's signs and symptoms could be explained by a systemic toxic reaction to either of these agents. Is either associated with cholestasis and was a liver biopsy considered?

DR. HEIMAN: Before that pertinent question was asked or answered, the patient was taken to the operating room. A percutaneous liver biopsy was not performed since the patient's toxic appearance was felt to warrant a laparotomy and cholecystectomy. She was observed to have a grossly normal gall bladder, normal bile ducts, and liver. No gall stones were found. A cholecystectomy and liver biopsy were performed.

On the first post-operative day the patient's fever reached 104°F and she developed an intense erythroderma. Blood cultures remained negative. An infectious disease consultation was requested. Physical examination revealed a well-nourished black woman resting in her surgical ICU bed in mild distress from incisional pain. She had diffuse erythema of her skin with pustular lesions on her arms and legs. There were no pustules on her palms or soles. Both her scalp and mucous membranes were normal. Scleral icterus and bilateral subconjunctival hemorrhages, which had not been present prior to surgery, were noted. The rest of her examination was remarkable only for the presence of a right-sided abdominal incision and some incisional tenderness. We concluded that fever, dermatitis, and jaundice were all secondary to chlorpropamide hypersensitivity and recommended stopping the antibiotics, since there was no evidence of infection.

DR. FRANK BIA (*Associate Professor of Medicine, Yale University School of Medicine*): What was most helpful to me and other members of our service was her history of rash and fever occurring after she began taking chlorpropamide and prior to being started on dicloxacillin. Shortly after beginning the chlorpropamide, she developed intense pruritus, which she unfortunately associated with her shampooing. The question just raised by Dr. Mellors was an important one in this case. Aware of previous reports describing rash and fever from chlorpropamide hypersensitivity, we looked into the question of cholestasis. In addition to intense pruritus, rash, and fever, chlorpropamide has been associated with cholestatic jaundice in 0.5 percent of patients given the drug. We felt confident about our recommendation to stop antibiotics immediately and begin a course of corticosteroids, especially in light of the normal gall bladder and bile ducts found at surgery. Had the ultrasound and HIDA examinations of gall bladder been normal, I suspect the physicians caring for this patient might also have felt more confident about ascribing this entire clinical picture to a drug reaction.

A PHYSICIAN: Isn't it possible that this patient simply passed a gall stone and had transient biliary obstruction on that basis?

DR. HEIMAN: I suppose that is a possible explanation for her jaundice; however, that would not explain her fever and cutaneous eruption. A hypersensitivity reaction to chlorpropamide explained all aspects of her presentation. Her antibiotics were stopped and she was begun on oral prednisone, 60 mg daily. The skin biopsy (Fig. 1) showed a superficial perivascular mixed-cell infiltrate. There was perifollicular infiltration as

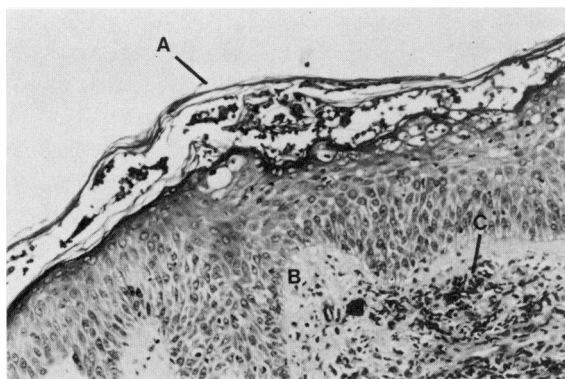


FIG. 1. Punch biopsy specimen of skin from right forearm showing acute pustular drug eruption (150 \times). Note the subcorneal pustule containing numerous eosinophils (A), papillary dermal edema (B), and extravasated red blood cells indicating hemorrhage into the dermis (C).

well. The epidermis had focal collections of polymorphonuclear leukocytes and eosinophils above the stratum granulosum and was most consistent with a drug hypersensitivity reaction.

The patient became afebrile after one day of steroid therapy and she remained afebrile during the remainder of her hospital stay. Dermatitis quickly improved, and erythroderma faded, although she eventually desquamated almost her entire skin surface. As her serum bilirubin fell and her jaundice resolved, her serum alkaline phosphatase level rose to a peak of 647 IU/L. Concomitantly, her amylase and lipase rose as high as 585 IU/dl and 24 IU/ml (normal < 1.5), respectively. During this time she had an excellent appetite and was feeling well. Prednisone was discontinued after four days of therapy because of concern that her rising serum amylase and lipase were related to steroid therapy. Her blood eosinophil count rose after prednisone was discontinued, reaching 4,200 cells/ μ l. A repeat abdominal ultrasound examination was normal except for the absence of a gall bladder. Within one month her serum alkaline phosphatase, amylase, and lipase had returned to normal.

The intraoperative liver biopsy showed mild chronic portal triaditis with inflammation confined to the portal areas. There was some fatty change and nuclear anisocytosis reflecting a nonspecific response to injury. There was no evidence of chronic active hepatitis or cirrhosis.

A PHYSICIAN: Had the chlorpropamide been discontinued immediately after admission?

DR. HEIMAN: Yes. However, it should not be surprising that her hypersensitivity reaction continued to evolve for several more days. The half-life of chlorpropamide is 36 hours. Dr. Robert Levine will discuss chlorpropamide hypersensitivity in more detail.

DISCUSSION

DR. ROBERT LEVINE (*Postdoctoral Fellow in Endocrinology, Yale University School of Medicine*): Chlorpropamide is an oral hypoglycemic agent in the sulfonylurea class of drugs. Shortly after chlorpropamide's release, in the late 1950s, several reports of jaundice and hepatic damage associated with its use appeared [1,2]. While these effects are listed in both the *Physician's Desk Reference* (PDR) and the manufacturer's literature, several current textbooks of endocrinology and diabetology either fail to consider them or mention them only in passing. A review of oral hypoglycemic agents

published in 1977 parenthetically noted a 0.5 percent incidence of transient cholestatic jaundice, but did not indicate whether therapy was continued [3,4].

As in the patient under discussion, the jaundice is generally cholestatic, with elevations of serum alkaline phosphatase out of proportion to the elevation of serum transaminases. This pattern could easily be misinterpreted as biliary obstruction. The onset of clinical symptoms tends to occur within two to five weeks of starting therapy, as in this case. Jaundice is frequently preceded or accompanied by high fever, toxic appearance, malaise, nausea, anorexia, and vague abdominal pains. In many cases there is a generalized erythematous maculopapular rash, which may progress to scaling or diffuse exfoliative dermatitis. In many cases peripheral blood eosinophilia has been noted [1].

The symptoms tend to resolve within a few days to a week of discontinuing the medication. However, biochemical abnormalities, including elevated alkaline phosphatase and bilirubin, may not return to normal for several weeks to a month, and even after stopping the medication, the laboratory abnormalities may worsen before they improve [1,2]. Liver biopsies done on patients with chlorpropamide-induced jaundice may show prominent bile stasis, particularly in centrilobular zones, with bile thrombi and degeneration of liver cells. Hepatic architecture remains intact, but areas of focal necrosis have been observed [5]. Some reports describe peri-portal inflammation including eosinophilic infiltration [5]. Electron microscopy has shown electron-dense mitochondrial inclusions, swollen and disrupted endoplasmic reticulum, dilated bile canaliculi, and altered microvilli in undilated bile canaliculi [5]. These findings are not always present, and in some cases biopsies are normal [2].

It is still unclear whether cholestasis reflects an allergic or a toxic reaction. The findings of a clinical latent period, rash, eosinophilia, and positive reactions following rechallenge with the drug all suggest an allergic mechanism; however, in some cases jaundice may occur without any of these associated findings. Whatever its mechanism, the pathologic abnormality seems to be one of altered bile canaliculus permeability, resulting in sludging, precipitation of bile salts, formation of bile plugs, and focal obstruction [5].

Recently two second-generation oral hypoglycemic agents were released in the United States: glyburide (Micronase, Diabeta) and glipizide (Glucotrol). Extensive European experience indicates that one of their advantages is a lower frequency of adverse reactions; hepatic toxicity rarely has been reported. In an early survey of over 5,000 patients receiving these drugs, there were few liver function abnormalities reported [6]. There has been one case report of cutaneous bullae and reversible cholestatic jaundice associated with glyburide therapy [7], and an additional report of fatal toxic erythema, jaundice, eosinophilia, and renal failure associated with necrotizing angitis [7]. Both cases appeared to have been idiosyncratic reactions, and second-generation agents continue to show a lower incidence of side effects [8,9].

It has been suggested that the lower incidence of side effects observed with the second-generation hypoglycemic agents may be due to their higher potency and lower serum levels, as well as fewer drug interactions. The first-generation agents are polar compounds which bind to albumin with ionic forces. Other anionic drugs such as coumadin, nonsteroidal anti-inflammatory agents, or sulfonamides may displace the first-generation agents from albumin, causing higher serum drug levels and hypoglycemia [10]. The second-generation agents are nonpolar, bind to albumin by non-ionic forces, and cause fewer drug interactions [10,11]. In addition, the "Antabuse

Syndrome," or facial flushing, which occurs in some patients who ingest alcohol while taking chlorpropamide, has rarely been observed in patients taking the second-generation hypoglycemic agents.

In summary, the clinical syndrome induced by the sulfonylureas, sulfonamides, or other drugs causing intrahepatic cholestasis may mimic biliary obstructive disease with symptoms of fever, toxicity, abdominal pain, nausea, vomiting, jaundice, and an elevation of serum alkaline phosphatase. A history of drug ingestion, or the presence of rash or eosinophilia, should raise suspicions of a drug reaction. Some sources have suggested routinely checking the patient's alkaline phosphatase levels during the first few weeks of chlorpropamide administration since the reaction is generally seen during the first six weeks of therapy.

A PHYSICIAN: Does cholestatic jaundice occur with tolazamide (Tolinase) administration?

DR. LEVINE: It does. While most frequently associated with chlorpropamide use, cholestatic jaundice has been reported with all of the first-generation oral hypoglycemic agents. One study investigated cross-reactivity between agents and found that some patients who had previously experienced chlorpropamide hepatotoxicity were able to tolerate tolbutamide (Orinase) [1]. Other investigators report cross-reactivity between agents [5].

A STUDENT: What about sulfa drugs, i.e., the commonly used antibiotics?

DR. LEVINE: Similar pictures have been described with the sulfonamides. Descriptions of sulfonylurea hepatotoxicity refer to the sulfonamides as the prototype for such reactions.

A PHYSICIAN: Would you warn her not to take any sulfa medications again? For example, should a urinary tract infection be so treated in the future?

DR. LEVINE: It would be best to consider her as having a sulfa allergy, especially with a reaction this severe. The severity of reported reactions is variable. Obviously the ones reported in the literature are among the most severe. However, there have been a number manifested only by transient abnormalities of liver function tests. Such patients don't present with the full clinical syndrome, and in these patients another drug of the same class might be cautiously tried.

DR. HEIMAN: This case is an excellent illustration of the necessity to consider drug hypersensitivity when a patient presents with an acute systemic illness, particularly if associated with a rash. Had the diagnosis of chlorpropamide-induced cholestasis and dermatitis been considered earlier in this case, the patient might have been spared a laparotomy and its associated risks.

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