We herein retrospectively analyze the cutaneous manifestations of 21 cases with primary biliary cirrhosis (PBC) during the past 12 years in our hospital. Among them, the most common skin manifestations of PBC is pruritus (61.9%), followed by jaundice (52.4%), xanthomas and xanthelasmas (33.3%), hyperpigmentation (14.3%), and lichen planus (4.8%). We also described three cases presenting as several types of xanthomas due to secondary hypercholesterolemia and hyperlipidemia in PBC. The relationship between lipoprotein disturbances and different types of xanthomas was identified. Types of xanthomas are valuable diagnostic markers of the underlying lipid and lipoprotein disturbances. In these patients, despite conventional dietary, drug, and plasmapheresis therapies, there was no improvement in the size and number of the xanthomas. Liver transplantation for decompensated chronic liver disease resulted in complete resolution of xanthomas in all our cases. It is a drastic but successful remedy for complications of abnormal lipid metabolism associated with primary biliary cirrhosis. (Dermatol Sinica 21: 304-316, 2003)

Key words: Xanthoma, Primary biliary cirrhosis, Liver transplantation
INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic, idiopathic, progressive, cholestatic liver disease that usually affects middle-aged women and eventually leads to liver failure.¹, ² The course of the disease usually extends over a period of 10 years or more. The early stage of PBC is typically insidious and marked by pruritus and fatigue. Subsequently, increasing pigmentation of the skin, jaundice, and steatorrhea are seen. Protraction of the cholestasis leads to decompensated hepatocellular disease and is manifested by hemorrhage, pathologic fractures due to osteoporosis, ascites, hepatic encephalopathy, and the formation of cutaneous xanthomas. Patients with PBC can develop xanthomas due to secondary hypercholesterolemia and hyperlipidemia.¹, ² Here we reviewed the skin manifestations of 21 patients with PBC diagnosed in recent 12 years and described 3 cases who had marked hyperlipidemia and several types of extensive xanthomatosis. The relationship between lipoprotein disturbances and different types of xanthomas was found. Despite multiple aggressive management, only liver transplantation could result in maintaining a sustained lipid lowering effect and resolution of xanthomatosis.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of all patients diagnosed as PBC in the National Taiwan University Hospital between January 1991 and December 2002. Totally, 21 patients were diagnosed as PBC under the following criteria: ① Alkaline phosphatase (ALP) more than 1.5 times the upper limit of normal, ② the presence of anti-mitochondrial antibody in the serum, ③ a compatible histologic appearance of a liver biopsy specimen, and ④ normal extrahepatic bile ducts by endoscopic retrograde cholangiography or operative cholangiography.²⁴ Pathological staging was performed according to Scheuer's classification.⁵ None of the patients had clinical evidence of coronary artery disease. The clinical courses and laboratory data of the three patients (case 1, 2, and 3) were regularly followed at our Dermatological Clinic. For the other cases, we reviewed and analyzed their medical records, and then telephoned them for checking the clinically relevant events.

STATISTICAL ANALYSIS AND RESULTS

The 21 patients were divided into two groups to study the relationship between the presentation of xanthomas and the clinical backgrounds. Group 1 was patients with clinical evident xanthomas (xanthelasma alone was excluded), while the group 2 was patients without xanthomas. The clinical backgrounds including sex ratio, age, serum immunoglobulin M (IgM) level, pathological staging of the liver biopsy and the plasma cholesterol level were recorded. All the variables were compared with the use of Fisher’s exact test or Wilcoxon rank sums test (SAS software, SAS Institute, Cary, N.C.).

RESULTS

The study group consisted of 21 patients (5 males and 16 females, 23.8% and 76.2% respectively) with varying severity of PBC recruited from the gastroenterological clinics of our hospital. The age ranged from 37 to 78 years old and the mean is 51.6. The clinical course had been variable. The brief clinical manifestations, lipid profiles and physical findings were summarized in Table I. The most common skin manifestations of PBC is pruritus
Table I. Summary of the clinical backgrounds of the 21 cases of PBC

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Follow-up period since diagnosis</th>
<th>Xanthomas</th>
<th>Xanthelasma</th>
<th>IgM</th>
<th>ANA</th>
<th>Liver biopsy stage</th>
<th>CHO level</th>
<th>TG level</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1#</td>
<td>F</td>
<td>49</td>
<td>5y</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>III</td>
<td>316-1503</td>
<td>240-812</td>
<td>P*, J, LP, F, BWL, Poor appetite, Steatorrhea</td>
</tr>
<tr>
<td>2#</td>
<td>F</td>
<td>43</td>
<td>3y8m</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>III</td>
<td>515-1100</td>
<td>215-538</td>
<td>J*, P, RUQ pain, F</td>
</tr>
<tr>
<td>3#</td>
<td>F</td>
<td>37</td>
<td>3y2m</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>III</td>
<td>610-1088</td>
<td>164-291</td>
<td>F*, J, P, BWL, Poor appetite, Dry eye</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>43</td>
<td>1y</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>II</td>
<td>536-1040</td>
<td>211-406</td>
<td>P*, J, RUQ pain, Poor appetite, BWL</td>
</tr>
<tr>
<td>5▲</td>
<td>F</td>
<td>55</td>
<td>16ys</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>III</td>
<td>432-745</td>
<td>148-232</td>
<td>P*, J, RUQ pain, Poor appetite, BWL</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>73</td>
<td>2y9m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>I</td>
<td>237-325</td>
<td>72-146</td>
<td>F*, BWL, Poor appetite</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>48</td>
<td>4m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>II</td>
<td>399-438</td>
<td>208-297</td>
<td>J*</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>36</td>
<td>2y1m</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>I</td>
<td>191-440</td>
<td>74-223</td>
<td>F*</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>47</td>
<td>1y9m</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>I</td>
<td>216-231</td>
<td></td>
<td>F*, Pale stools</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>57</td>
<td>9y</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>II</td>
<td>130-255</td>
<td>65-103</td>
<td>F*, Poor appetite, BWL</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>38</td>
<td>2y3m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>II</td>
<td>190-262</td>
<td>124-166</td>
<td>Steatorrhea*</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>56</td>
<td>3y1m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>II</td>
<td>295-427</td>
<td>122-161</td>
<td>P*, F</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>51</td>
<td>6y7m</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>II</td>
<td>227-397</td>
<td>105-234</td>
<td>P*, F</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>42</td>
<td>4y10m</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>II</td>
<td>217-422</td>
<td>72-282</td>
<td>P*, F</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>40</td>
<td>4y6m</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>II</td>
<td>249-417</td>
<td>147-378</td>
<td>P*, J, F, Hyperpigmentation</td>
</tr>
<tr>
<td>16#</td>
<td>F</td>
<td>78</td>
<td>11y4m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>III</td>
<td>140-273</td>
<td>63-106</td>
<td>P*, J, F, Poor appetite, Dry eye, BWL, EV</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>68</td>
<td>3y6m</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>IV</td>
<td>172-211</td>
<td>92-114</td>
<td>BWL, F, Poor appetite, Dry eye, EV</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>48</td>
<td>5y7m</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>IV</td>
<td>265-297</td>
<td>153-271</td>
<td>P*, J, F, Hyperpigmentation</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>52</td>
<td>7y</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>I</td>
<td>183-210</td>
<td>68-126</td>
<td>P*, J, BWL, Poor appetite</td>
</tr>
<tr>
<td>20#</td>
<td>F</td>
<td>62</td>
<td>10y</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>IV</td>
<td>196-257</td>
<td>41-190</td>
<td>P*, J, BWL, Poor appetite</td>
</tr>
<tr>
<td>21▲</td>
<td>F</td>
<td>61</td>
<td>9y5m</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>IV</td>
<td>152-352</td>
<td>69-181</td>
<td>P*, BWL, F, EV, Hepatic encephalopathy</td>
</tr>
</tbody>
</table>

# Patient had received liver transplantation
▲ Current status: Dead
* = First symptom

Antibodies and IgM at the time of diagnosis (ANA: antinuclear antibodies)

Liver biopsy stage:
I: chronic non-suppurative destructive cholangitis;
II: portal inflammation with ductular proliferation;
III: fibrosis
IV: cirrhosis

CHO: cholesterol, TG: triglycerides
P: pruritus, J: jaundice, LP: lichen planus
BWL: body weight loss, F: fatigue, RUQ: right upper quadrant EV: esophageal varices
followed by jaundice (11 cases, 52.4%), hyperpigmentation (3 cases, 14.3%), and lichen planus (1 case, 4.8%). In 10 patients, generalized pruritus is the first symptom (47.6%) and jaundice in 3 (14.3%). These two cardinal symptoms coexist in 10 patients (47.6%). In 7 cases with xanthomas or xanthelasmas, three cases developed both xanthomas and xanthelasmas, two cases only had xanthomas, and two cases had xanthelasmas alone. As compared with the group 2 (16 cases) with no xanthomas, the group 1 (5 cases) with xanthomas had a statistically significant relationship with the total cholesterol level exceeding 450 mg/dL for more than 3 months (0% vs 100%, p=0.000491). Comparing the group 1 and group 2 patients including the sex ratio, age distribution, IgM level, and pathological staging of the liver biopsy, patients with more advanced PBC (III, IV) had a higher risk in developing xanthomas. (Odds ratio = 8.8 [95% confidence interval 0.77~100.26]) (Table II). The plasma cholesterol levels were elevated in patients with all stages of PBC, except 2 patients (case 17 and 19). The positive antinuclear antibody (ANA) and elevated IgM levels were noted in 57% and 67% of the patients respectively, but there was no evidence that patients with elevated serum levels of these antibodies had a higher frequency of histological or biochemical features suggestive of chronic active hepatitis. The clinical xanthoma type, clinical presentation, the lipoprotein disturbances and histories of the five cases are described and summarized in Table III. Patients 1-3 developed widespread xanthomas 7 months to 12 months after the initial presentation symptoms or signs of PBC. Xanthomas and xanthelasmas, if concurrently developed, appeared at about the same time. The appearance and disappearance of the various xanthomata in the presenting patients were closely correlated with the level of lipid profile (Table III). Five of our patients underwent orthotopic liver transplantation for advanced PBC.

**CASE REPORT**

**Case 1**

A 49-year-old woman admitted in December 1997 had had generalized pruritus, jaundice, fatigue and body weight loss for 10 months. At that time, liver function tests revealed total bilirubin 19.4 mg/dL (normal 0.2-1.2), direct bilirubin 15.0 mg/dL (normal 0-0.4), AST 96 U/L (normal 5-31), ALT 64 U/L (normal 0-31), and ALP 1088 U/L (normal 64-238). Serology tests to hepatitis viruses B, C and D were all negative. The ANA was positive with a titer of 1:1280 (speckled type).
and the antimitochondrial antibody was also positive (1:20). The serum IgM level was 405 mg/dL (normal 160.57±72.21). The liver biopsy showed the findings consistent with PBC. On the basis of the above findings, PBC was diagnosed.

In January 1998, numerous pinhead-to-ricegrain-sized yellowish papules with some-
what reddish hue were noted on the whole body. At that time, the cholesterol and triglycerides (TG) levels were 317 mg/dL (normal 130-220) and 812 mg/dL (normal 130-220), respectively. Eruptive xanthomas were diagnosed. The skin lesions resolved gradually in the following 2 months with change of the lipid profile to cholesterol 562 mg/dL and TG 359 mg/dL. In July 1998, she developed several pea-to bean-sized, itching, violaceous polygonal patches and plaques scattered over the trunk and limbs without affecting the oral and genital mucosae. A skin biopsy from a lesion on the left thigh showed a diagnosis of lichen planus (LP) with xanthomatous changes. About 1 month later, a gradual onset of generalized tuberoeruptive xanthomas on the patient’s trunk and extremities (Fig. 1A) as well as planar xanthomas mimicking palmar crease xanthomas (Fig. 1B) over the palms were noted. Most of the earliest xanthoma lesions developed on the preceding LP lesion sites. At that time, the lipid profile of the patient was total cholesterol 648 mg/dL, high-density lipoprotein (HDL) 26 mg/dL (normal > 35), low-density lipoprotein (LDL) 369 mg/dL (normal <150), very-low-density lipoprotein (VLDL) 253 mg/dL (normal <40) and TG 538 mg/dL. A low-fat diet

Fig. 1A
Tuberoeruptive xanthomas on the calf of case 1.

Fig. 1B
Planar xanthomas of case 1, shown here on the palms. Unlike palmar crease xanthomas, they are well-demarcated plaques that extend beyond the palmar creases.
and simvastatin were administered in addition to cholestyramine and ursodiol to treat her PBC with secondary hyperlipidemia and xanthomas. Her cholesterol level still progressively increased with persistent development of new xanthoma lesions in the following 6 months. There were various types of xanthomas including tuberoeruptive, tuberous, planar xanthomas mimicking palmar crease xanthomas and tendonous xanthomas. She underwent plasmapheresis for three times during January 1999 and there was no improvement in either the cholesterol, LDL and TG levels or in the size and number of the xanthomas. She received an orthotopic liver transplantation in March 1999 and the postoperative course was relatively uneventful.

Seven months after the transplantation, her serum bilirubin was 0.4 mg/dL, AST 15 U/L, ALT 10 U/L, cholesterol 222 mg/dL, TG 284 mg/dL. The lipoprotein levels were also nearly normal. The xanthomas improved quickly after the transplantation and was completely resolved within 12 months (Fig. 1C).

Case 2
A 43-year-old woman had been well until 5 years previously when she had generalized pruritus and fatigue followed by slight anorexia and mild jaundice in January 1998. In conjunction with the clinical and serological evidences including a positive antimitochondrial antibody (1:20), serum IgM 609.0 mg/dL and ALP 2350 U/L, a liver biopsy in April 1999 confirmed the diagnosis of PBC (Stage III).

In September 1998, multiple pea-to beansized, red-yellow papules and nodules developed on her face, palms, forearms, elbows, and feet. Xanthelasmas and tuberous xanthomas were diagnosed (Fig. 2A). A skin biopsy from a lesion on the right palm revealed a circumscribed tumor in the dermis composed of nests of foamy histiocytes. The lipid profile indicated the total cholesterol 752 mg/dL, TG 215 mg/dL, HDL 22 mg/dL, and LDL 687 mg/dL.
About 6 months later, a gradual onset of tendinous xanthomas affecting her Achilles tendons was noted (Fig. 2B). At that time, the lipid profile of the patient was total cholesterol 946 mg/dL, TG 405 mg/dL, HDL 25 mg/dL, LDL 840 mg/dL. There was no objective improvement in either the levels of cholesterol and TG or in the size of the xanthomas, though ursodiol and cholestyramine were administered. She had ever undergone plasmapheresis for three times in July 2000, but the xanthomas persisted. She received an orthotopic liver transplantation in August 2000, and recovered rapidly. After the surgery, the liver function tests normalized, and the lipid profile checked 3 months after transplantation showed the cholesterol 215 mg/dL, TG 165 mg/dL. The lipoprotein levels were also nearly normal. The number and size of xanthomas decreased quickly after the transplantation and all the xanthomas completely resolved within 3 months after the surgery.

**Case 3**

A 37-year-old woman with established PBC (stage III) of 3 years' duration had presented initially generalized malaise, jaundice and tea-colored urine in December 1998. Multiple pea-to bean-sized, itching, painful, yellowish...
nodules were noted initially on the bilateral finger creases in January 2000. The painful and itching lesions spread to the palms, soles, ears, elbows and buttocks as well as progressed in size over the ensuing 6 months. Fine motor activity of her hands was affected and the plantar nodules were painful even without pressure leading to interference of sleep. A skin biopsy from a lesion on the left thumb revealed a band-like foamy histiocyte aggregation mixed with lymphocytes in the upper dermis (Fig. 3). Oil red and Sudan III stains both showed positive staining. Planar xanthomas mimicking palmar crease xanthomas and tuberoeruptive xanthomas were diagnosed. At that time, the lipid profile of the patient indicated the total cholesterol 1088 mg/dL, HDL 43 mg/dL, LDL 610 mg/dL, and TG 404 mg/dL. She also had bilateral xanthelasmas (Fig. 4). She received a low-cholesterol, low-fat diet as well as ursodiol and cholestyramine.

After 2 years of therapy, the plasma cholesterol level decreased from 1088 to 404 mg/dL, and the plasma TG level from 178 to 112 mg/dL. She had some symptomatic improvement in the discomfort of her hands and feet. There was no objective decrease in the size of the xanthomas. She underwent an orthotopic liver transplantation in August 2002. Two months after the transplantation, her serum

Fig. 3
The infiltrate of upper dermis consisted mainly of foamy histiocytes and a few inflammatory cells, left thumb. (A) (H & E, X 100), (B) (H & E, X 400).

Fig. 4
Xanthelasmas on the periorbital areas of case 3.
bilirubin was 0.9 mg/dL, AST 26 U/L, ALT 17 U/L, cholesterol 192 mg/dL, TG 122 mg/dL. The lipoprotein levels were also nearly normal. The xanthomas improved quickly after the transplantation and completely resolved within 2 months except the xanthelasma lesions.

DISCUSSION

The onset of PBC typically occurs between the age of 30 and 65, and 90% of the patients were women. In our series of 21 patients, the average age is 51.6 years old. 76% of our patients were women. Gradual onset of pruritus followed by jaundice is by far the most frequent presentation. Reviewing the literature, the common cutaneous manifestations of PBC in the order of frequency are pruritus, jaundice, hyperpigmentation, xanthomas, and rarely lichen planus. Our study of 21 patients also showed a similar clinical skin presentations except hyperpigmentation and xanthomas, which showed more cases of developing xanthomas than those of developing hyperpigmentation in our series. Fatigue is noted in up to 78% of patients. Seventeen of our patients presented with fatigue (81%).

PBC is a chronic, cholestatic liver disease, hallmarked by progressive, inflammatory destruction of the intrahepatic bile ducts. Current evidences suggests that the tissue injury observed may be related to an autoimmune pathogenesis. Plasma levels of cholesterol, TG, and phospholipids are often elevated in patients with PBC. Therefore, patients with PBC can develop several types of xanthomas due to secondary hypercholesterolemia and hyperlipidemia. The liver is the major site of lipoprotein synthesis, and the hepatic LDL receptors removes 70% of the LDL from the plasma. The serum free-cholesterol also increases due to a decreased hepatic synthesis of lecithin:cholesterol acyltransferase, which is the major intravascular cholesterol esterifying factor in plasma. The cholesterol elevations are often accompanied by increases in LDL and decreases in HDL concentrations.

The plasma cholesterol levels are elevated in at least half of the PBC patients and may exceed 1000 mg/dL in PBC patients with xanthomas. Four of our patients with xanthomas had the cholesterol levels exceeding 1000 mg/dL. A standardized assessment on 85 patients with PBC within 1 year of developing symptoms revealed 22% of the patients had cutaneous xanthomas. In our series, 23.8% of the patients developed xanthomas within one year after diagnosing PBC.

Many types of xanthomas appear in longstanding hypercholesterolemia: if the plasma cholesterol levels are greater than 450 mg/dL for more than 3 months, such lesions invariably ensued. Patients 12 and 14 have had the total cholesterol level as high as 450-480 mg/dL for two months. It seems that the period of time during which they had cholesterol exceeding 450 mg/dL was short, which may explain the failure of developing xanthomas. Spontaneous regression of generalized tuberous xanthomas, coincident with a sustained decrease of the plasma cholesterol levels below 450 mg/dL with a good response to the diet and drug therapies was observed in patient 5. Under these conditions, almost complete resolution of the xanthomas occurred within 2 years in patient 5. The duration of elevation of the serum lipids is an important factor. Xanthomas are composed almost exclusively of foam cells, which are believed to represent the tissue macrophages that have phagocytosed the lipid components of lipoproteins deposited in tissues. Xanthomas are now considered to be reactive lesions to altered lipid metabolism. Recent evidence has demonstrated transport of serum lipoproteins through endothelial membranes and then phagocytosed by the foam cells. These lipoproteins are then degraded to lipids and stored in vacuoles. Capillary microleakage of lipoproteins enhanced by tissue trauma and subsequent phagocytosis by the dermal histiocytes could lead to the formation of xanthomas in patients with hyperlipidemia. Thus areas subjected to stress, friction or injury, particularly the extensor surfaces, buttocks, tendons, and skin creases...
have a predilection for xanthoma formation.\textsuperscript{14} Xanthoma has been classified into eruptive, tubereroeruptive, tuberous, tendinous, or planar xanathomas on the basis of clinical morphology, anatomic distribution, and the mode of development.\textsuperscript{14} The development of xanthomas in areas previously affected by erythroderma\textsuperscript{15} or chronic inflammatory skin diseases\textsuperscript{16} further supports that local tissue factors might play a role in the formation of xanthomas. In case 1, Chu et al. also hypothesize that the damage to basal keratinocytes in LP lesions accompanied by systemic hypercholesterolemia could lead to the development of xanthomas in LP lesions.\textsuperscript{6}

The correlations of clinical xanthoma types and the lipid profile are discussed and the lipoprotein component that accumulates in tissues is the critical determinants of the types of xanthomas.\textsuperscript{14} It will provide a causal explanation for the specific relationship between lipoprotein disturbances, lipid profile and types of xanthomas. Types of xanthomas are valuable diagnostic markers of the underlying lipid and lipoprotein disturbances for dermatologists.\textsuperscript{14, 17} Eruptive xanthomas are a sign of chylomicronemia and elevated plasma level of VLDL. Tendinous xanthomas are seen almost always exclusively in disorders characterized by elevated plasma levels of LDL or altered forms of LDL. Tuberoeruptive xanthomas develop as a result of deposition of chylomicron remnants, VLDL, VLDL remnants, or components of these lipoproteins in tissues (thus elevated TG and cholesterol), whereas xanthomas at the tuberous end of the spectrum are the result of accumulation of LDL, VLDL remnants, or their components. Planar xanthomas are also characteristic of disorders that cause hepatic cholestasis, such as PBC and biliary atresia.\textsuperscript{14} In these conditions, free cholesterol cannot be excreted properly into the bile and is instead regurgitated into plasma, where free cholesterol binds with albumin and phospholipid to form an abnormal lipoprotein called lipoprotein X. Infiltration of the lipoprotein X or its components into the dermis and subcutaneous tissue is probably responsible for the development of planar xanthomas.\textsuperscript{14} On the palms they can be differentiated from the palmar crease xanthomas by their plaque appearance (rather than a diffuse macular discoloration), extension beyond the creases, and evolution in a grayish or dusky hue.\textsuperscript{14}

In our described 3 cases, all of them had tubereroeruptive, tuberous, and planar xanthomas that were related to the elevated plasma cholesterol level (LDL) or concurrent elevation of cholesterol and TG (LDL, VLDL). However, case 1 showed an episode of eruptive xanthomas during January to March 1998. At that time, her lipid profile revealed TG 812 mg/dL and cholesterol 317 mg/dL, which was compatible with the previous report that patients with early histologic stages of PBC presented with mildly elevated VLDLs and LDLs, marked elevation of HDLs and TG.\textsuperscript{4} In contrast, patients with advanced disease had marked elevation in cholesterol and LDLs with the presence of lipoprotein-X, and a significant decrease in HDLs.\textsuperscript{4}

Severe hypercholesterolemia associated with chronic intractable cholestasis presents a difficult management problems.\textsuperscript{19} Recently, ursodiol treatment (13 to 15 mg/kg) has been reported to achieve both a symptomatic improvement and an "improvement" in serum biochemical markers in patients with clinically overt PBC.\textsuperscript{7} Although the mechanism of the protracted pruritus is not entirely clear, cholestyramine, an oral bile salt-sequestering resin, may be helpful in a dosage of 8 to 12 g/d to improve both pruritus and the hypercholesterolemia.\textsuperscript{7} Cholesterol may also be lowered by reducing dietary fat or increasing dietary polyunsaturated fatty acid.\textsuperscript{7} Short-term plasmapheresis has been demonstrated to have a beneficial effect on hyperlipidemia and pruritus in patients with PBC.\textsuperscript{7} In patients with chronic cholestasis who undergo successful liver transplantation, the cholestatic syndrome is no longer present and the cholesterol and apoprotein synthesis could be normalized.\textsuperscript{7} In the presenting case 3, though diet and drug therapy lowered the levels of cholesterol and TG, the size of the xanthomas did not decrease.
Plasmapheresis has successfully decreased the number and size of xanthomas in some but not all patients with PBC. In the presenting cases receiving plasmapheresis (case 1 and case 2), however, there was no decrease in the size of xanthomas although large amounts of cholesterol were being removed temporarily during the procedure.

The natural history of PBC is usually progressive over many years. The disease course in the 3 described cases of our patients progressed inevitably and at the time of liver transplantation, they all had an end-staged liver disease associated with ascites and portal hypertension with variceal bleeding. They all tolerated liver transplantation well and their plasma lipid levels normalized after the operation. The most impressive thing was the speed with which xanthomas resolved after liver transplantation: 2 months to 12 months later.

In a patient with PBC, if complications of the xanthomas are making the quality of life intolerable and cannot be ameliorated by conventional therapeutic approaches, liver transplantation would be the best treatment. In patients with advanced PBC who undergo liver transplantation for other indications, it can be expected that this procedure will normalize the serum lipid abnormalities and lead to the resolution of xanthomas.

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REFERENCES


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