Angiokeratoma Corporis Diffusum in a Patient With No Recognizable Enzyme Abnormalities

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Background: Angiokeratoma corporis diffusum is a clinical variant of angiokeratoma that is typically associated with an enzyme deficiency in the metabolism of glycoprotein, most notably Fabry disease, resulting in many other systemic manifestations.

Observations: We report a case of angiokeratoma corporis diffusum that did not have an identifiable enzyme deficiency. A review of the literature revealed few similar cases.

Conclusion: Angiokeratoma corporis diffusum without recognizable enzyme deficiencies appears to be a distinct clinical entity with a benign course.

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Angiokeratomas are hyperkeratotic papules that are characterized histologically by superficial ectatic vessels with epidermal proliferation. They occur clinically as 1 of 5 different subtypes. Angiokeratoma corporis diffusum (ACD) occurs most typically on the lower region of the trunk, buttocks, and thighs and is usually associated with an underlying enzyme deficiency in the metabolism of glycoproteins. For many years, this term was used synonymously for Fabry disease, a systemic X-linked disease caused by a deficiency of the lysosomal enzyme α-galactosidase A. Angiokeratoma corporis diffusum is now known to occur in several other diseases related to deficiencies of enzymes that are involved in the metabolism of glycoproteins, including fucosidosis, sialidosis, mannosidosis, GM1 gangliosidosis, and Kanzaki disease. Very rarely, ACD has been reported in patients with normal enzyme activity. We report such a case not only with normal enzyme activity but also without evidence of any underlying systemic abnormalities. We also review the other reported cases of ACD with normal enzyme function.

REPORT OF A CASE

A 33-year-old man presented with complaints of red-purple papules in his groin that had been increasing in size and frequency since puberty. He reported that the lesions had first appeared on his elbows and knees in childhood but had then begun to develop on his penis, scrotum, buttocks, and inguinal area during puberty. These papules, although otherwise asymptomatic, caused him great cosmetic concern. They continued to increase in size and number throughout puberty and during his 20s.

The patient had no other significant medical history, specifically no renal, cardiac, or neurologic disease. A review of systems was negative for acral pain, paresthesias, edema, fever, cough, orthopnea, dyspnea, chest pain, and palpitations. The findings of his physical examination, apart from his skin, were unremarkable. His intelligence was normal to above average. He is married with 1 healthy son and has no significant family history of similar skin lesions or renal, cardiac, or neurologic disease. He works as a physician’s assistant.

His skin examination revealed multiple 2- to 7-mm, red to purple, hyperkeratotic and coalescing papules on his penis, scrotum, lower abdominal area, and inguinal region and on the proximal aspect of his thighs. Similar lesions, approximately 1 to 2 mm in diameter, were evident on his knees and elbows (Figure 1 and Figure 2).

A biopsy specimen of one of the papules on his penis revealed compact orthokeratosis, epidermal acanthosis, and superficial ectatic and dilated capillaries lined by normal-appearing endothelial cells (Figure 3). Electron microscopy showed normal endothelial cells with no enlarged or laminated lysosomes (Figure 4). Enzyme analysis of a sample of our patient’s leukocytes showed normal activity of α-D-galactosidase A for Fabry disease (1.2 nmol/min per milligram of
protein; reference range, 0.6-2.0 nmol/min per milligram of protein). The levels of other enzymes, including α-N-acetylgalactosaminidase (Kanzaki disease), α- and β-D-mannosidase (α- and β-mannosidosis), β-D-galactosidase (GM1 gangliosidosis), and α-L-fucosidase (fucosidosis), were also within normal limits. Because of the normal activity found in the enzymes analyzed, gene mutational analysis was not performed.

Blood workup revealed that the serum urea nitrogen and creatinine levels, liver function, and complete blood cell count were within normal limits. A complete ophthalmologic examination, including slit-lamp evaluation, demonstrated only minimal neovascularization in the limbus but no whorled corneal opacities or lens abnormalities. The results of dipstick urinalysis were also normal. Although microscopic urinalysis did not show any casts, cells, crystals, or active urinary sediment, lipid globules, with their characteristic “Maltese crosses,” were noted on polarization (Figure 5). This latter test was repeated in a latex- and powder-free environment, with similar re-

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**Figure 1.** Multiple hyperkeratotic, vascular papules in classic “bathing trunk” distribution.

**Figure 2.** Inguinal area showing additional angiookeratomas.

**Figure 3.** Histopathologic examination shows compact orthokeratosis, acanthosis, and ectatic capillaries (original magnification ×10).

**Figure 4.** Electron microscopy reveals normal endothelial cells with no abnormal lysosomes.

**Figure 5.** Polarized microscopy of urine sample reveals several “Maltese crosses.”
results. Our patient was treated with a 532-nm diode laser under diascopy, with excellent cosmetic results.

### COMMENT

Several different clinical variants of angiokeratomas exist. Solitary angiokeratomas typically appear on the lower extremities and are typically larger and sometimes more verrucous than other angiokeratoma variants. Multiple angiokeratomas with a clinical appearance similar to the solitary variant have also been described. Angiokeratoma of Mibelli is characteristically found on the dorsum of the hands and feet. Angiokeratomas of Fordyce are found mostly on the scrotum or vulva and are often described in middle-aged to elderly men. Angiokeratoma circumscriptum occurs as a solitary plaque of grouped papules.²

The ACD variant was first described in 1898 in 2 independent articles.¹³ Although controversy exists as to who described the entity first, the term ACD was, in fact, used synonymously with α-galactosidase A deficiency, also known as Fabry disease (occasionally referred to as Anderson-Fabry disease).²⁶ Fabry disease is an X-linked deficiency of the lysosomal enzyme α-galactosidase A, which is involved in the catabolism of glycosphingolipids. Its systemic manifestations are related to the accumulation of glycosphingolipids in, among others, endothelial cells.²⁶⁻²⁸

In addition to Fabry disease, ACD has been associated with other enzyme defects including GM1 gangliosidosis (β-galactosidase deficiency), fucosidosis (α-fucosidase deficiency),⁹ Kanzaki disease (α-N-acetylgalactosaminidase deficiency),¹¹⁻¹⁴ β-mannosidosis (β-mannosidase deficiency),¹⁰ and sialidosis (sialidase deficiency). Apart from X-linked Fabry disease, all of these lysosomal enzyme defects are inherited in an autosomal recessive fashion, and they are all characterized by some degree of central nervous system dysfunction, a characteristic facies, and often mental retardation and organomegaly.²⁶⁻²⁸

To our knowledge, there have been 10 previously reported cases of ACD associated with “normal” enzyme function (Table). Although not all cases were confirmed by electron microscopy or a complete enzyme analysis, the clinical presentation, lack of systemic symptoms, and laboratory data all fit with this idiopathic type of ACD. It is difficult, however, to include the case of Laxmisha et al,²⁴ since neither enzyme analysis nor electron microscopy was performed. It is possible that in their case enzyme deficiency was present but had not yet manifested itself clinically. Also, it appears as though Calzavara-Pinton et al,²² have described a unique and separate entity with underlying arteriovenous malformations and an autosomal dominant type of inheritance. Finally, it is plausible that the case described by Nguyen et al,²⁵ may have more accurately been classified as multiple angiokeratomas, given the lesions’ lower limb predominance, verrucous nature, and large size. Angiokeratoma corporis diffusum has more classically been described as occurring “between the bellybutton and the knees.”

Most cases described no systemic disease or dysmorphic facies characteristic of glycoprotein metabolism enzyme deficiencies. Exceptions include the case of

### Table. Cases of Angiokeratoma Corporis Diffusum With Normal Enzyme Function

<table>
<thead>
<tr>
<th>Source</th>
<th>Age at Onset, y/Sex</th>
<th>Systemic Findings</th>
<th>Enzymes Analyzed</th>
<th>Electron Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al,¹⁹ 1984</td>
<td>34/M</td>
<td>None</td>
<td>α-Galactosidase A, β-0-galactosidase, α-fucosidase, sialidase</td>
<td>Normal</td>
</tr>
<tr>
<td>Crovato and Rebora,¹⁶ 1985</td>
<td>8/F</td>
<td>Obesity</td>
<td>α-Galactosidase A, β-0-galactosidase, α-L-fucosidase</td>
<td>Not done</td>
</tr>
<tr>
<td>Marsden and Allen,¹⁷ 1987</td>
<td>28/M</td>
<td>None</td>
<td>α-Galactosidase A, α-fucosidase, α-mannosidase, β-glucosidase, sphingomyelinase, β-galactosidase, β-hexosaminidase, β-galactocerebrosidase, aroylsulfatase A, α-iduronidase, α-glucuronidase, sialidase</td>
<td>Normal</td>
</tr>
<tr>
<td>Frappaz et al,²⁰ 1987</td>
<td>13/M</td>
<td>None</td>
<td>α-Galactosidase A, β-0-galactosidase, α-fucosidase</td>
<td>Normal</td>
</tr>
<tr>
<td>Pravata et al,²³ 1990</td>
<td>10/F</td>
<td>None</td>
<td>α-Galactosidase A, β-0-galactosidase, α-fucosidase</td>
<td>Not done</td>
</tr>
<tr>
<td>Gerbig et al,²¹ 1995</td>
<td>3/F</td>
<td>Mental impairment, dysmorphic facies</td>
<td>Sialidase, β-0-galactosidase, α-mannosidase, α-fucosidase, α-0-galactosidase, sphingomyelinase</td>
<td>Normal</td>
</tr>
<tr>
<td>Calzavara-Pinton et al,²² 1995</td>
<td>(3-Generation family with 7 members)</td>
<td>Arteriovenous fistulas, autosomal dominant pattern</td>
<td>α-Galactosidase A, β-0-galactosidase, α-fucosidase, α-sialidase (in some patients)</td>
<td>Normal (4 patients evaluated)</td>
</tr>
<tr>
<td>Firmani et al,²³ 1997</td>
<td>26/M</td>
<td>None</td>
<td>α-Galactosidase A, β-0-galactosidase, α-fucosidase</td>
<td>Normal</td>
</tr>
<tr>
<td>Laxmisha et al,²⁴ 2003</td>
<td>22/M</td>
<td>None</td>
<td>Not done</td>
<td>Normal</td>
</tr>
<tr>
<td>Nguyen et al,²⁵ 2004</td>
<td>27/M</td>
<td>Hypertension, gout, sleep apnea, obesity</td>
<td>α-0-acetylgalactosaminidase, β-0-galactosidase, α-0-mannosidase, α-L-fucosidase, α-0-galactosidase</td>
<td>Normal</td>
</tr>
<tr>
<td>Present case</td>
<td>12/M</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Gasparini et al,20 which apparently coincidentally occurred in a young woman with Turner syndrome, and that of Gerbig et al,21 in which the symptoms were attributed to complications of asphyxia during childbirth. Although our patient showed no symptoms or physical examination findings suggestive of underlying enzyme deficiency, he did have lipid globules in his urine sample on polarized microscopy. These findings were found on another microscopic examination in a latex-free environment. The pathogenesis of these angiokeratomas in the absence of enzyme deficiency, such as in this case, is unclear. It may represent a partial deficiency or enzyme mosaicism. Supporting evidence for this might include the appearance of lipid droplets in the urine from another otherwise healthy kidney and the lower (but within normal range) levels of enzymes in some of the above-mentioned patients or their first-degree relatives.17,19 Perhaps gene mutation analysis could be helpful in this regard, as over 200 mutations have been described in Fabry disease alone.27 Alternatively, our patient’s lipid droplets may represent a very early manifestation of a glomerular disorder, such as minimal change disease.28 Regardless, his renal function will need to be monitored.

The case reported herein represents the 10th reported case of ACD associated with normal enzyme activity in which there are also no systemic abnormalities that can be attributed to disorders of glycoprotein metabolism. The cases described by Calzavara-Pinton et al22 are not included because many of them involved systemic arteriovenous fistulas and appeared to be a distinct autosomal dominant disease (Table). Also, the case by Laxmisha and colleagues has not been confirmed, as neither electron microscopy nor enzyme analysis was performed. Angiokeratoma corporis diffusum with normal enzyme activity appears to be a distinct entity with a benign course. Underlying enzyme deficiencies should be ruled out using leukocyte and/or fibroblast analysis in combination with electron microscopy. Laser therapy can be an effective treatment option for patients with ACD.

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