Case Report

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Diagnosis of vitamin K-dependent coagulation factors deficiency assists in the management of skin findings of pseudoxanthoma elasticum-like disease: A case report

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Abstract

This report outlines that patients with Pseudoxanthoma elasticum-like disorder with multiple coagulation factor deficiency, which is an autosomal recessive disease with hematological, dermatological, ophthalmic, and cardiovascular manifestations, can receive aesthetic treatment. Patients usually report bleeding tendencies and extensive skin folds in the flexural areas. Our patient in particular had profound skin folds in the neck, chest, arms, abdomen, and thighs, and had a bleeding diathesis. Surgical correction of the cutaneous manifestations has not been attempted until the time of writing this report, thus we report the first surgical correction of the skin folds associated with this disease, which was possible after the diagnosis of combined deficiency of vitamin K-dependent coagulation factors. Aesthetic surgery to patients with the disorder may be possible as long as the bleeding tendency is managed using appropriate measures.

Keywords: Pseudoxanthoma elasticum, GGCX, vitamin K, factor deficiency, aesthetic surgery, bleeding.

Introduction

Hereditary combined vitamin K-dependent coagulation factor deficiency (VKCFD) is an extremely rare autosomal recessive disorder characterized by hemostatic and non-hemostatic clinical manifestations. The non-hemostatic symptoms include skeletal abnormalities, osteoporosis, cardiac abnormalities, retinopathy, loss of dermal elasticity, and early onset arteriosclerosis [1]. VKCFD results from genetic variants affecting two genes, GGCX, which causes VKCFD type 1, and VKORC1, which causes VKCFD type 2 [1]. Pseudoxanthoma elasticum-like disorder with multiple coagulation factor deficiency (PXE-like) is caused by homozygous or compound heterozygous mutations in the GGCX gene [2,3]. Cutaneous manifestations in PXE-like include brownish macules and generalized skin folds and laxity [2,3]. Pseudoxanthoma elasticum (PXE) is a different disease caused by a different gene mutation that is indistinguishable from PXE-like on Light Microscopy (LM) [4]. Here we report a case of Pseudoxanthoma elasticum-like disorder with coagulation factor deficiency and, to our knowledge, the first successful surgical correction of the disease's cutaneous manifestations in which the coagulation factor deficiency was managed with prothrombin complex concentrate.

Case Report

I. Patient Information

We report a 22 years old female born to consanguineous unaffected parents, whose concerns were the generalized skin folds and the bleeding diathesis. The patient had ecchymoses, hemarthroses, menorrhagia (managed with hormone replacement therapy), and generalized skin folds in the neck, chest, arms, abdomen, and thighs. The patient was previously diagnosed with Factor VII deficiency and her bleeding episodes were treated with recombinant factor (VIIa). The patient has had an appendectomy, for which she was prepared with the appropriate amount of VIIa.

II. Hematological Assessment

The patient first presented with left lower quadrant abdominal pain, clinical and ultrasound examination revealed a cyst on the left ovary. A surgical approach was planned to excise the cyst, for which prothrombin time (PT) and partially activated thromboplastin time (PTT) were done and both were prolonged (Table 1). Our hematological assessment of the bleeding disorder revealed the diagnosis of VKCFD (Table 1) and the planned surgery was canceled. After the diagnosis of VKCFD, the prescribed drug for treatment of bleeding episodes is PCC.

Table 1: *Hematological lab assessment.*

Test	Value	Reference
Prothrombin Time (PT) INR	79.6 sec (7.5%) 6.36	Control: 12.5 sec (100%) Patient to Control Ratio: 6.36
Partially activated Thromboplastin Time (PTT)	55.8 sec	Control: 31 sec Patient to Control Ratio: 1.8
Bleeding Time (Duke's method)	2.5 min	< 6 min
Factor-VII	8.2%	55-170%
Factor-IX	2.7%	60-150%
Factor-X	11.2%	70-120%

III. Skin Evaluation

The occurrence of VKCFD, the presence of generalized skin folds, and consanguinity between the patient's parents lead to the assumption of PXE-like and thus it was necessary to perform a full skin evaluation. Skin symptoms started developing in synchronous with menarche. At the age of 14 years, skin folds developed in the neck, then a year later in both arms and axillae (Figure 1), six months after that skin folds appeared in the abdomen, and finally at the age of 21 the same skin folds appeared in both thighs. All skin folds reached a state after which they did not proceed. A full thickness skin biopsy was taken

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under local anesthesia from the skin of the right lower quadrant, to prevent excessive bleeding she was prescribed 5000 units of aPCC for the procedure. LM with Hematoxylin and eosin staining revealed normal epidermis and abnormal basophilic densities in the dermis which was most compatible with PXE (Figure 2), and Alcian Blue staining, along with the patient's VKCFD, confirms the diagnosis of PXE-like disorder with coagulation factor deficiency (Figure 3).

IV. Evaluation of the Skeletal System

Patient's facial appearance was similar to reported cases [2,5], midfacial hypoplasia and flat nasal bridge were noted. The patient's height was measured and found to be shorter than expected (patient's height was 146 cm and the mean parental height was 160 cm). At the age of 22 she fractured her ankle due to a minor trauma, and she also fractured her 5th metatarsal only two months after the first fracture. Bone profile tests and bone mass density (BMD) were consistent with osteoporosis caused by vitamin D deficiency (Table 2), however similar BMD results were reported in patients with PXE-like [6], thus osteoporosis in this patient may be explained by both vitamin D deficiency and by the PXE-like disease.

Table 2: *Bone mass density and bone profile tests.*

Test	Value	Reference
BMD Z-score (L_1-L_4) Z-score (left hip)	 -3.0 -2.4	Normal > -1.0 Osteopenia -1.0 to -2.5 Osteoporosis < -2.5
Albumin	4.3 g/dl	3.5-5.5 g/dl
Calcium Corrected calcium	9.1 mg/dl 9.34 mg/dl	8.5-10.5 mg/dl
Phosphate (fasting)	3.2 mg/dl	2.5-4.5 mg/dl
Alkaline Phosphatase (ALP)	187 IU/L	30-130 IU/L
25-hydroxycholecalciferol	8.02 ng/ml	Deficient < 25 ng/ml

V. Aesthetic Surgery

Brachioplasty of both the arms was planned as a start of a series of aesthetic surgeries. 2500 units of PCC were administered preoperatively to prevent excessive bleeding, and 1000 units of PCC were administered daily for eight days postoperatively to ensure good wound healing. Surgery outcomes were satisfactory to the patient and intraoperative bleeding was comparable to a patient without VKCFD or PXE-like, follow-up visits after four and nine months showed no change in the outcome or relapse (Figure 4).

Figure 1: *Arm and axilla before brachioplasty.*

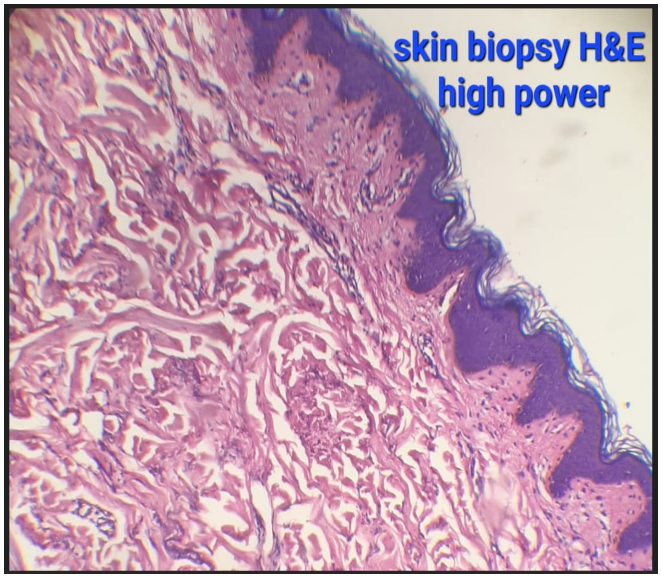

Figure 2: *Scattered basophilic spots are seen in the mid-dermis, which are most likely depositions of calcium.*

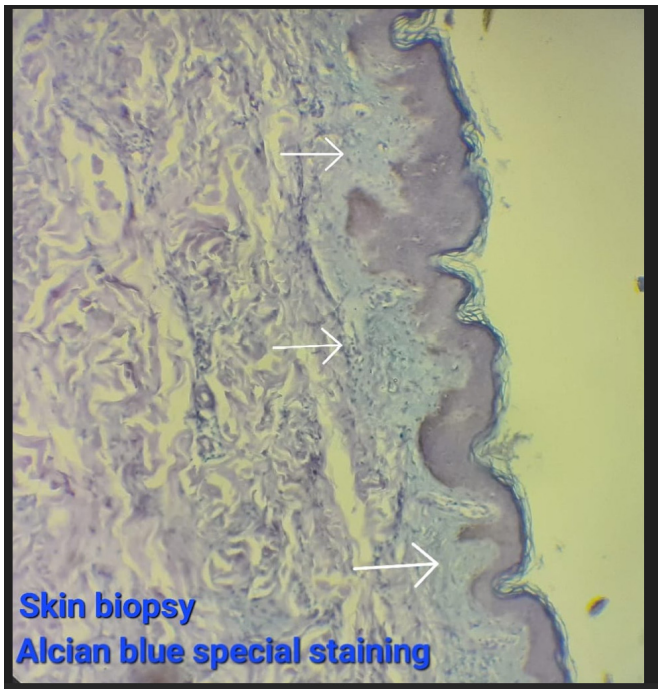

Figure 3: *Basophilic mucoid material in dermis stained positive for Alcian blue (arrows).*

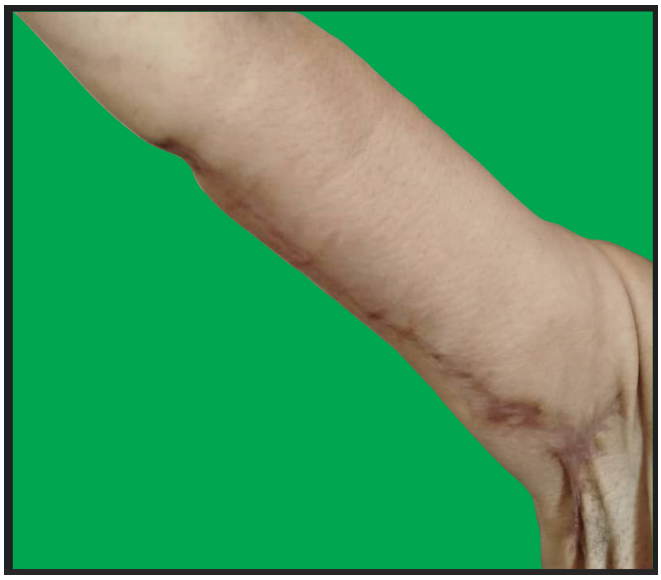

Figure 4: *Arm after brachioplasty.*

Discussion

The decision to perform the surgery on this patient could not be made without the diagnosis of VKCFD, which permitted the diagnosis of PXE-like disease, because it is not rational to perform aesthetic surgery without the identification of the causal disease behind the cosmetically unsightly appearance. Genetic analysis of the GGCX gene was not done, but the diagnosis of PXE-like disease was done by combining the cutaneous, hematological, and histopathological findings in this patient. Histopathological staining was not done with von-kossa stain or orcein stain, which were used in other published cases [2,3,5], but rather by Alcian blue stain which stains positive for mucoid material in PXE [7]. Factor-II was not measured along with other vitamin k-dependent coagulation factors. The patient did not receive vitamin k replacement because it was not available orally in the region, and parenteral access is not appropriate for this patient. Vitamin k replacement should be the treatment of choice to correct plasma levels of coagulation factors, prevention of bleeding, and cessation of the progression of the skeletal and cutaneous manifestations of the disease. Weekly doses of vitamin k (ranging from 70 mcg to 140 mg) is effective in raising factor levels [6]. Oral vitamin k (10mg two to three times per week) reduces the risk of hemorrhages [1]. We were not able to find long-term studies that correlate vitamin k supplementation in patients with PXE-like to the progression of skin findings or skeletal abnormalities or BMD.

Osteoporosis in this patient should not be solely explained by the vitamin d deficiency but also by the vitamin k deficient state (PXE-like disease) because vitamin k function is also needed for posttranslational carboxylation of other proteins, namely, Osteocalcin, which plays an important role in calcium metabolism and bone mineralization. Furthermore, numerous studies have shown that the concentrations of undercarboxylated osteocalcin is inversely correlated with BMD [8,9] and positively associated with bone fraction rate [8,10]. Patients with PXE-like disease should receive aesthetic surgery when needed and vitamin k replacement to correct coagulation factor levels and reduce bleeding risk and their BMD should be assessed and treated appropriately.

Contributorship Statement

Tahani Ali provided hematological consultation and reviewed the manuscript, Manal Mouhamad provided dermatological consultation and reviewed the manuscript, and Abdullah Almasri and Hala Alhalabi wrote the manuscript and collected the data.

Patient Perspective

For years, I suffered from excessive bleeding and the progressive skin folds. After my doctors accurately diagnosed the cause of my illness which permitted them to do the aesthetic surgery on me and provide me with the appropriate treatment for the bleeding episodes, I feel more like a normal person without the disease.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article. The data is only available in the archives of the Syrian Hemophilia Society.

Ethics Approval

Ethical approval was sought from the ethics council of the Syrian Hemophilia Society.

Informed Consent

Written informed consent was obtained for anonymized patient information to be published in this article. The consent form is supplied as an additional file for review but not for publication.

Conflict of interests

The authors declare no conflict of interests (COI) and COI disclosures from the four authors are supplied as additional files for review but not for publication.

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Declaration of Generative Artificial Intelligence and Artificial Intelligence-Assisted Technologies

The authors declare no use of any Artificial Intelligence Generated Content (AIGC) tools such as ChatGPT and others based on large language models (LLMs) used in developing any portion of the manuscript.

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