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Case report

PSEUDOXANTHOMA ELASTICUM AT HUE CENTRAL HOSPITAL

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ABSTRACT

Background: *Pseudoxanthoma Elasticum (PXE) is a rare disease with autosomal recessive inheritance. Dysfunctional or absent ABCC6 results in low serum PPi, ectopiccalcification, obviously of elastic tissue, eyes, and blood vessels. Clinical signs of PXE usually begin in early childhood, and skin changes are frequently the earliest sign of PXE. These skin lesions tend to progress slowly. PXE is related to the risk of blindness and peripheral vascular compromise. We present a case of a male patient who is possiblydiagnosed Pseudoxanthoma Elasticum at Hue Central Hospital.*

Case report: *A 20 - year - old male patient came to our clinic to check his skin lesions. According to him, the lesions appeared when he was 13 years old. Small flesh-colored papules appeared sparsely first at theperiumbilicaland abdominal areas with the changing size from 1-5mm. Gradually, such papular lesions coalesced to form bigger papules or plaques, and new skin lesions appeared symmetrically on abdomen, chest, twoarmpits, two arms and two groins. These lesions progressed slowly in years with no signs of inflammation or ulceration. Moreover, the patientdid not feel painful or itchy sensations. After conducting the skin biopsy, the patient was expected to have Pseudoxanthoma Elasticum (PXE) disease, and he was transferred to the related departments for examination.*

Conclusion: *The recognition of PXE is extremely important because it is associated with the risk of blindness and peripheral vascular compromise. The faster the detection and setting of diagnosis are made, the more extreme the preventive measures and the surveillance to prevent and control the progression of the disease are applied.*

Keywords: *Pseudoxanthoma Elasticum, PXE, ABCC6.*

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I. INTRODUCTION

Pseudoxanthoma Elasticum (PXE) is a rare disease with autosomal recessive inheritance. The gene or proteinaffected by the mutationis ATP-binding cassette subfamily C member 6 (ABCC6/ ABCC6) [1,2].

Although its specific substrate is still unknown, ABCC6 is involved in the homoeostasis of serum Pyrophosphate (PPi) - a main inhibitor of ectopic calcification. Dysfunctional or missing ABCC6 results in low serum PPi and ectopic calcification [2]. The effects of calcification are most apparent in the elastic tissues in the skin, eyes and blood vessels [3], including changes of skin, retina, gastrointestinal and cardiovascular systems [4].

The prevalence of PXE is estimated range from

1/100.000 to 1/25.000, with a predominance of female [4,5].

Clinical signs of PXE usually begin in early childhood [5]. Skin changes are frequently the earliest sign of PXE, and they tend to progress slowly. PXE is related to the risk of blindness and peripheral vascular compromise; therefore, early PXE detection is extremely important to prevent systemic complications, especially as those seen in the cardiovascular system [5].

According to our knowledge, Pseudoxanthoma Elasticum is a rare disease. Therefore, we report a case of a patient who came to Dermatology Department of Hue Central Hospitalfor examination and was possibly diagnosed PXE. In this way, our aim is to help dermatologists can recognise the skin lesions of PXE, early detect and set up tight surveillance measures of the disease progression.

II. CASE REPORT

A 20 - year - old male patient came to Dermatology Clinic of Hue Central Hospital to check his skin lesions in November 2020.

According to his history of present illness, the patient said that the lesions appeared when he was 13 years old. Small flesh - colored papules appeared sparsely first at the periumbilicaland abdominal areas with the changing size from 1 - 5mm. He did not feel painful or itchy sensations. Gradually, such papular lesions coalesced to form bigger papules or plaques, and new skin lesions appeared symmetrically on abdomen, chest, two armpits, two arms and two groins. These lesions progressed slowly in years.

There was nothing special about his family medical history. Neither his siblings nor his relatives had this disease.

In terms of clinical signs, the lesions were flesh-colored papules, plaques with the changing size from 1 - 10mm, distributing symmetrically on abdomen, periumbilical region, chest, two armpits, two arms and two groins, giving the skin a “cobblestone” or “gooseflesh” appearance. Some skin lesions sparsely appeared on the posterior side of the neck. These lesions had no signs of inflammation or ulceration. He did not feel painful or itchy sensations. Checking his oral mucosa revealed nothing abnormal.

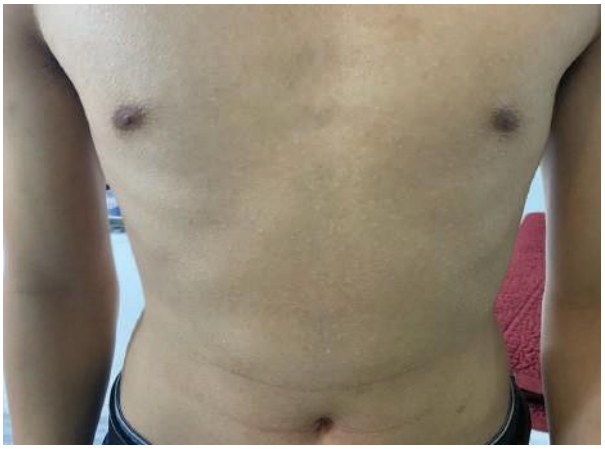

Figure 1: Flesh - colored papules, plaques with the size from 1 - 10mm, distributing symmetrically on abdomen, periumbilical region and chest

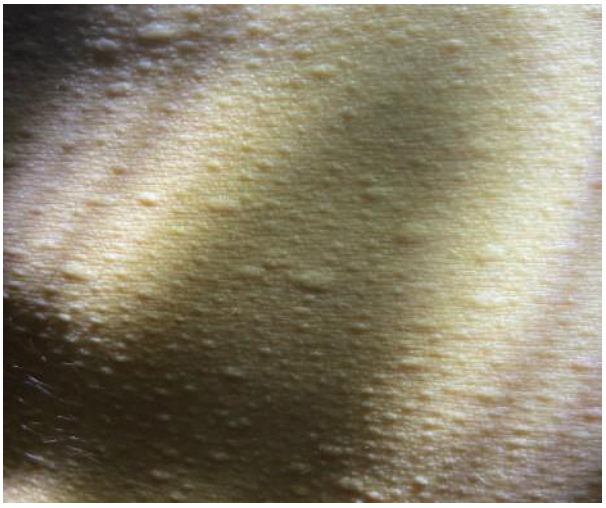

Figure 2: Flesh - colored papules, plaques with the size from 1 - 10mm, distributing symmetrically on abdomen, periumbilical region and chest

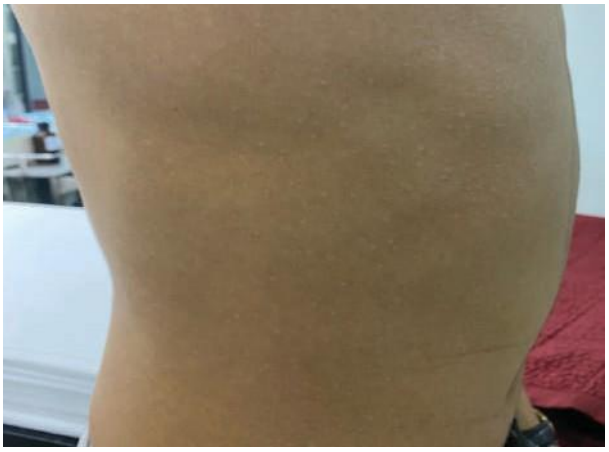

Figure 3: Flesh - colored papules, plaques with the size from 1 - 10mm, distributing symmetrically on abdomen

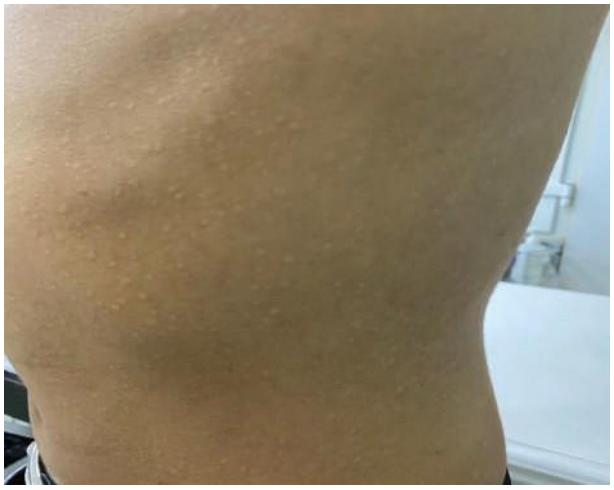

Figure 4: Flesh - colored papules, plaques with the size from 1 - 10mm, distributing symmetrically on abdomen

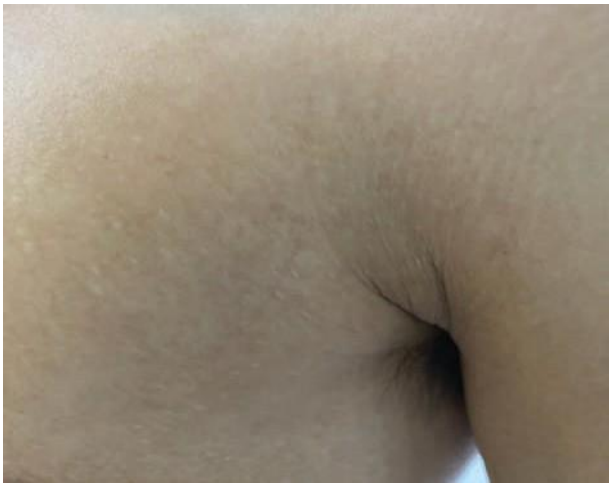

Figure 5: Small flesh - colored papules sparsely distribute on two armpits

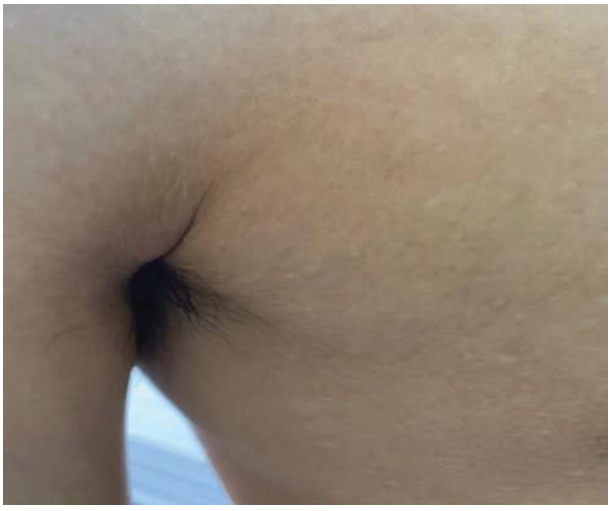

Figure 6: Small flesh - colored papules sparsely distribute on two armpits

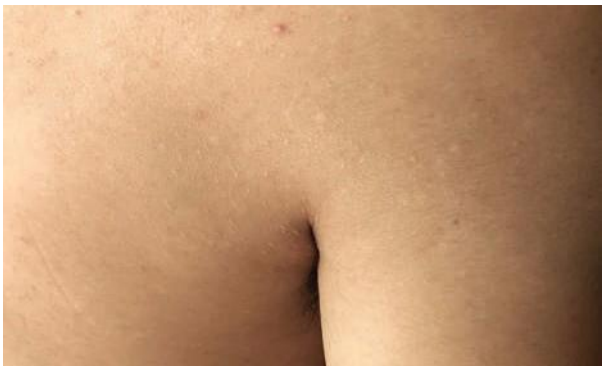

Figure 7: Small flesh - colored papules sparsely distribute on two armpits

Figure 8: Small flesh - colored papules sparsely distribute on posterior side of the neck

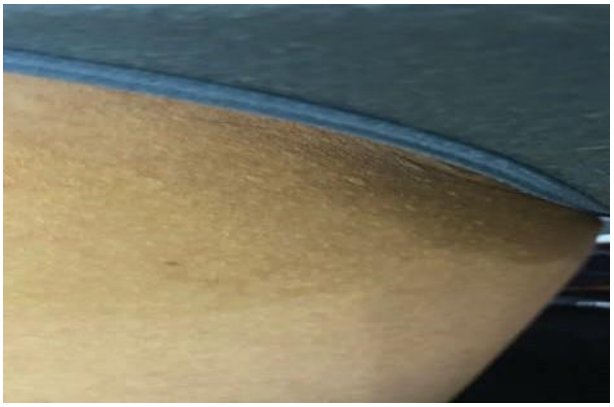

Figure 9: Small flesh - colored papules sparsely distribute on two groins

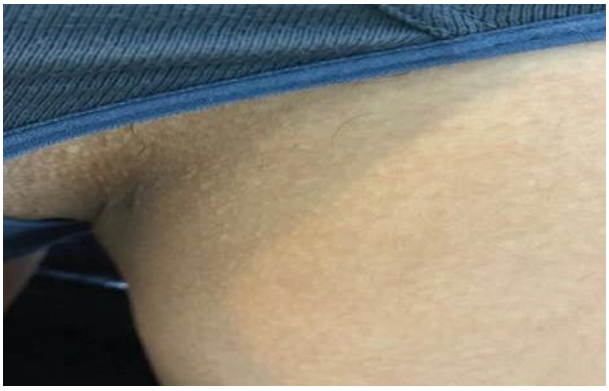

Figure 10: Small flesh - colored papules sparsely distribute on two groins

We conducted a biopsy of the patient's skin lesions, and the sample was taken from the abdomen with the size 0.1 cm. Microscopic description showed that damaged elastic fibers changed to blue - violet color due to calcium deposition, loss of dermis papillae, and underneath were collagen bundles disintegrating in many directions; the skin surface was lined with benign squamous epithelium with mild hyperpigmentation; no malignant changes were seen.

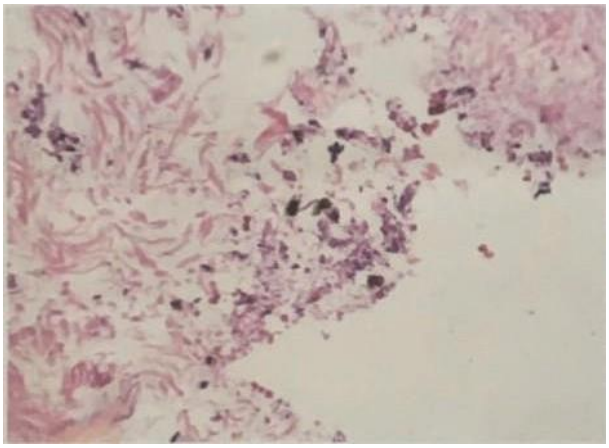

Figure 11: Skin biopsy: Damaged elastic fibers changed to blue-violet color due to calcium deposition, loss of dermis papillae, and underneath were collagen bundles disintegrating in many directions; the skin surface was lined with benign squamous epithelium with mild hyperpigmentation; no malignant changes were seen

Based on clinical and histopathological features, we expected the patient might have Pseudoxanthoma Elasticum disease.

We explained the nature and progression of the disease to the patient. In terms of Dermatology, we also offered methods that can treat skin lesions to improve aesthetic aspect. However, with the large extent of the skin lesions, the methods were almost impossible to perform. Then, the patient was referred to the relevant departments at our hospital for evaluation and doing tests according to each specialty. At Ophthalmology department, the patient was performed visual acuity test, refractive index measurement, fundus imaging, posterior segment OCT, and there was nothing abnormal. At Cardiology department, the patient was checked and administered to do electrocardiogram, Doppler echocardiography, but no abnormalities were detected.

In summary, we recommended regular monitoring to detect early signs of vision loss or secondary choroidal neovascularization, as well as to prevent other complications that were likely to develop with the progression of the disease. However, unfortunately, the patient did not have the routine check - up as we advised.

After 16 months, we contacted the patient and persuaded him to come back for a re - examination. The skin lesions remained stable and progressed slowly. The ophthalmology and cardiovascular status were not abnormal.

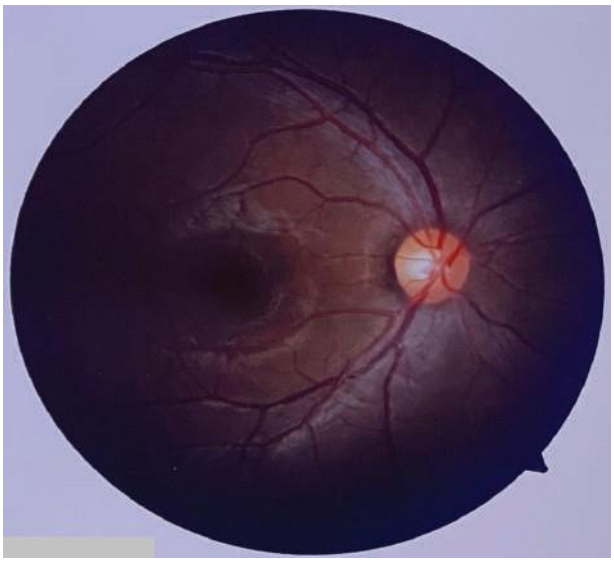

Figure 12: Fundus imaging revealed nothing abnormal

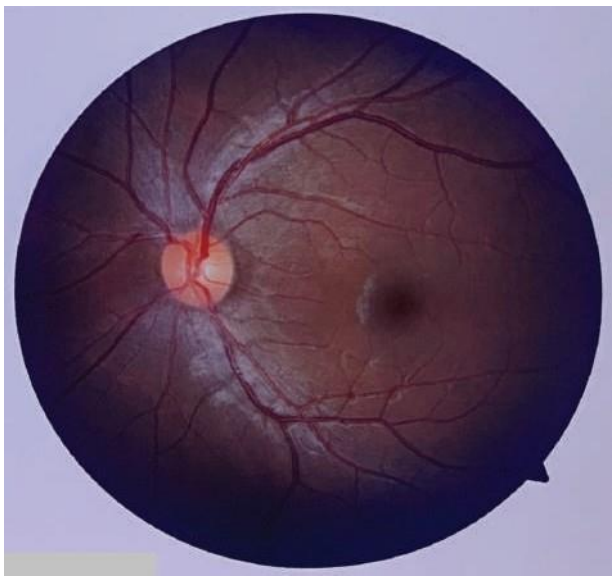

Figure 13: Fundus imaging revealed nothing abnormal

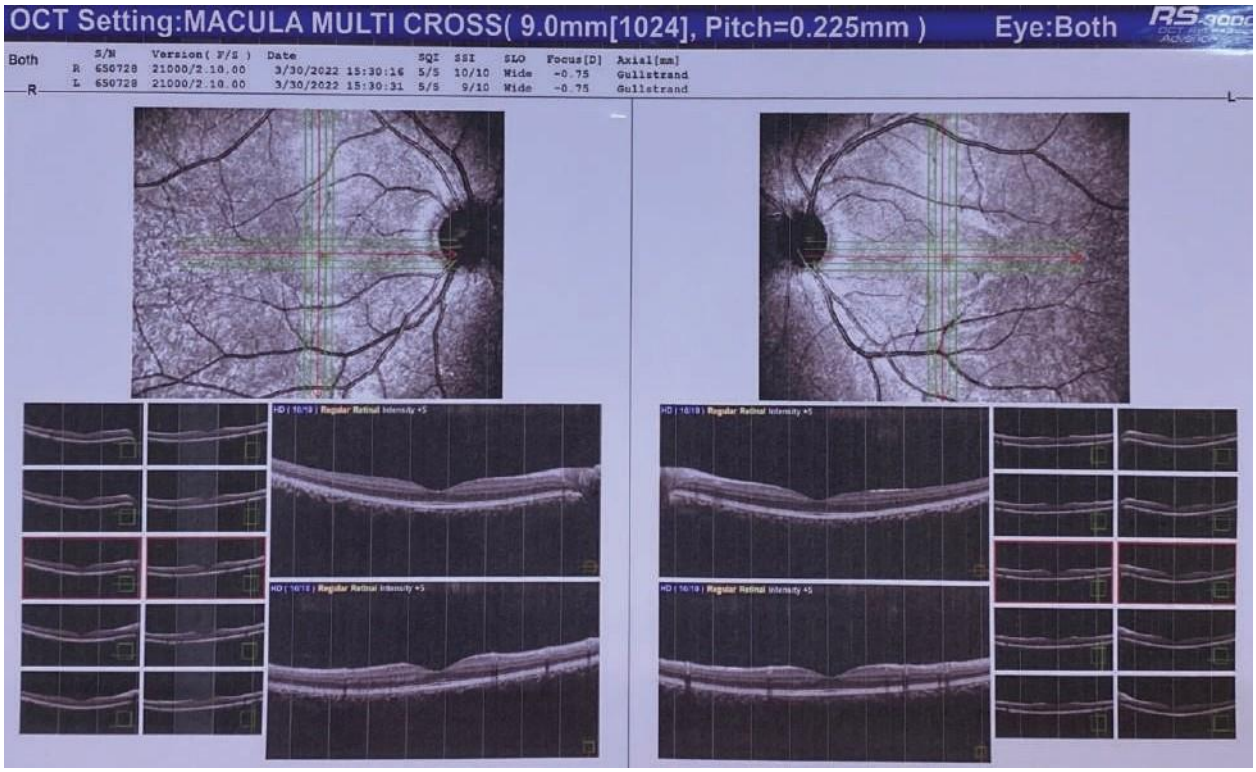

Figure 14: Posterior segment OCT image revealed nothing abnormal

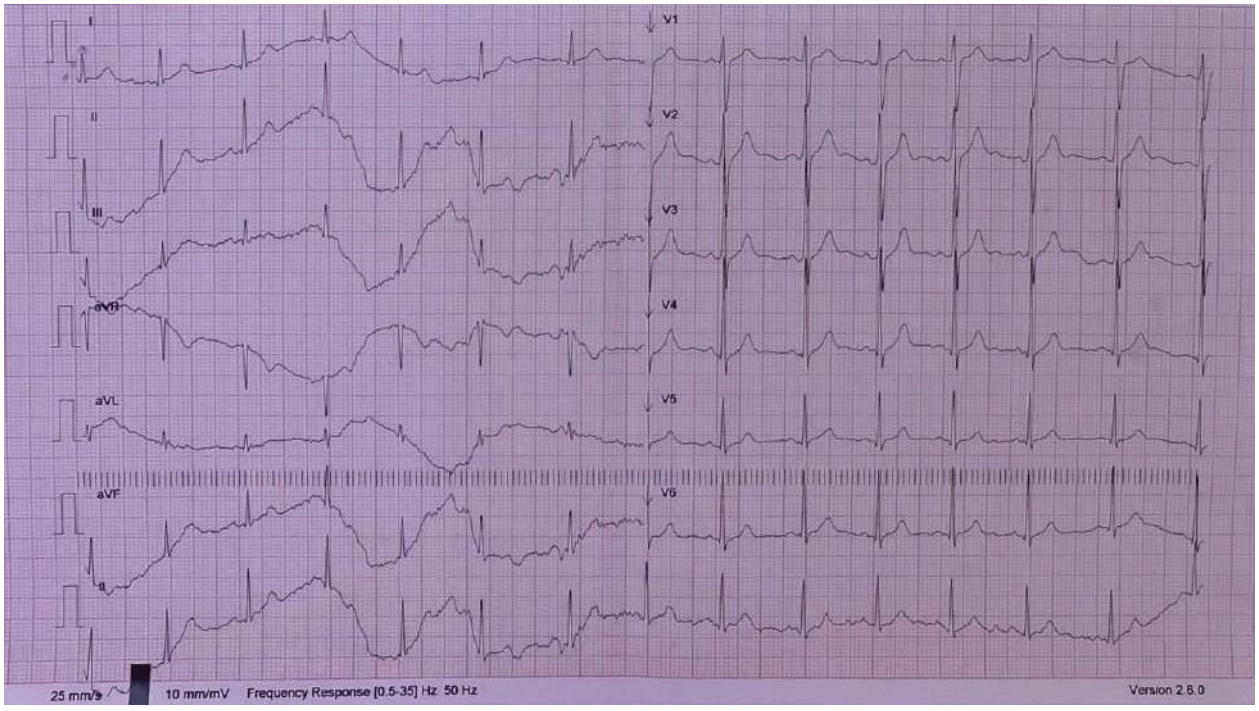

Figure 15: Electrocardiogram image revealed nothing abnormal

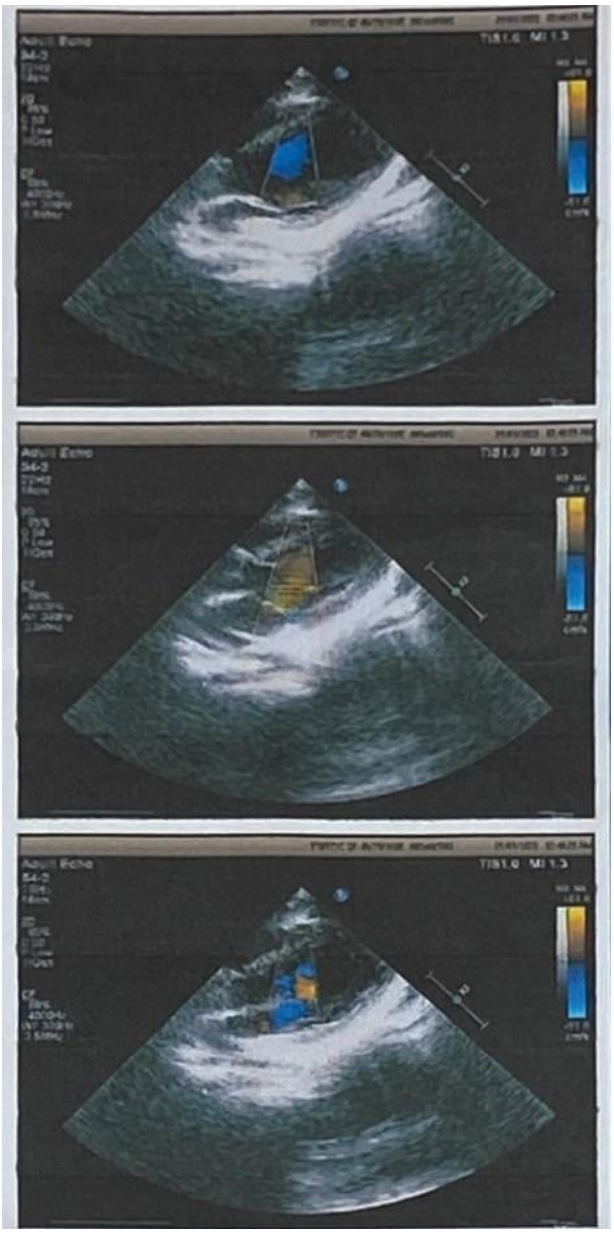

Figure 16: Doppler Echocardiography image revealed nothing abnormal

III. DISCUSSION

Pseudoxanthoma Elasticum (PXE) is a rare disease with autosomal recessive inheritance. The gene or protein affected by the mutation, ATP - binding cassette subfamily C member 6 (ABCC6/ ABCC6), is an Adenosine triphosphate (ATP) - dependent transmembrane transporter, which is mainly expressed in the liver and kidneys, but also, to a minor degree, in peripheral tissues [1,2].

ABCC6 is encoded by the ABCC6 gene located on chromosome 16, location p 13.1. Although its specific substrate is still unknown, ABCC6 is involved in the homoeostasis of serum Pyrophosphate (PPi), a main inhibitor of ectopic calcification. Dysfunctional or missing ABCC6 results in low serum PPi and, thus, ectopic calcification, especially of soft connective tissue [2].

The effects of calcification are most apparent in the elastic tissues in the skin, eyes and blood vessels [3]. Effects may include skin changes, changes in the retina of the eye that may result in significant loss of central vision, changes in the cardiovascular system that may involve calcification of arteries and decreased blood flow in the arms and legs, and changes in the gastrointestinal system that may lead to bleeding in the stomach or intestines [4].

The prevalence of PXE is estimated range from 1/100.000 to 1/25.000, with a predominance of female [4,5].

Clinical signs of PXE usually begin in early childhood [5]:

Skin changes: Skin changes are frequently the earliest sign of PXE, and they tend to progress slowly. At first, small yellow or flesh - colored papules with changing diameter of up to 10 mm localize on the nape and sides of the neck and in flexural areas (such as the axillae, the antecubital fossae, and periumbilical, inguinal and popliteal areas) [1,3]. Such papular lesions tend gradually to coalesce to form plaques with a cobblestone appearance [6]. Then, these plaques of skin become lax and redundant, mainly localize around the neck and flexural areas of the main joints, but also into oral, vaginal, and rectal mucosae [2,3]. Although the skin alterations are mostly asymptomatic, there are a few cases of perforating PXE, characterized by chronic or recurrent ulceration of skin lesions [2]. Some authors suggested that the presence of horizontal and oblique mental creases before the age of 30 years is specific for PXE [3].

This description also applies to our patient. The lesions began when the patient was 13 years old with the appearance of small flesh - colored papules sparsely first atperiumbilicaland abdominal areas, and then new skin lesions appeared symmetrically on abdomen, chest, two armpits, two arms and two groins. These lesions progressed slowly in years, and they coalesced to formbigger plaques with a cobblestone appearance.

Eyes: The underlying pathology is the progressive calcification and friability of Bruch's membrane. Brunch's membrane is located between the retinal

pigment epithelium and the choriocapillaris, acting as a physiological barrier against capillaries growing into the retina. Progressive calcification leads to breaks in the Bruch's membrane, which are visible as angioid streaks in fundoscopy. A progressive loss of function of the Bruch's membrane means that choroidal neovascularization passes through the Bruch's membrane, especially in the macular region [2]. Neovessels and retinal haemorrhages result in macular symptoms (metamorphopsia, scotoma), peripapillary atrophy, disciform macular or foveal scarring, and definitive central visual loss [6,7]. However, the earliest ocular finding in PXE is the presence of "peau d'orange" [7].

Cardiovascular system: PXE may result in calcification and vessel narrowing, and small and middle sized arteries are mainly involved [6,8]. This can lead to early atheromatosis, hypertension, acute myocardial infarction, cerebrovascular accident and peripheral arterial occlusion [8].

Gastrointestinal system: peripheral vessel calcification and other vascular changes may lead to gastrointestinal bleeding with the increasing risk of death [5]. Bleeding usually occurs in the stomach or intestines [4].

The diagnosis and classification of PXE is to date not widely accepted and remains ambiguous in some cases.

The consensus conference in 1994 classified PXE based on histopathology and clinical features of skin, eyes, including criteria [1,4]: Major criteria: Characteristic skin signs: Yellow cobblestone lesions in flexural areas. Characteristic histological features of lesional skin: Elastic tissue and calcium or von Kossa stains. Characteristic ophthalmologic features: Angioid streaks, peau d'orange, or maculopathy - In adults > 20 years old. Minor criteria: Characteristic histological features of non - lesional skin: Elastic tissue and calcium or von Kossa stains. Family history of PXE in first - degree relatives.

The latest diagnostic criteria and classification for PXE were established in 2014 [7]: Definitive PXE: Two pathogenic mutations in the ABCC6; OROcular findings - angioid streaks > 1 DD or peau d'orange in an individual < 20 years of age; Together with. Skin findings: Characteristic pseudoxanthomatous papules and plaques on the neck or flexural creases OR; Diagnostic histopathological changes in lesional skin: Calcified elastic fibers in the mid and lower dermis, confirmed by positive calcium stain. Possible PXE: Without having met the above criteria, a patient could be considered to have "possible PXE", the degree of probability depending on the presence of other factors, including family history and particularly affected siblings; microcalcifications in arterial blood vessels and other organs; histopathological changes in apparently unaffected skin; presence of a single PXE - associated mutation in either ABCC6 or ENPP1, especially if the same mutation has been found in an affected sibling.

Accordingto this criteria, the typical skin lesions, even when confirmed by histopathology, can not confirm the diagnosis of PXE without the detection ofocular lesions. In this case, the diagnosis is likely to be "Possible PXE" [7]. Our patient is suitable for this diagnosis.

To this day, there is no specific treatment, and the therapeutical management is based in prevention, tracking and monitoring of complications associated with the disease [8].

In this report, we mainly discuss possible methods for skin lesions for aesthetic improvement. Data on the treatment of skin lesions in patients with PXE are scarce. Three different approaches have been reported: cosmetic surgery, injection of collagen, and resurfacing of the skin by using a Fractional CO_2 Laser [2].

Cosmetic surgery: There are a few case reports about a subcutaneous rhytidectomy and neck skin lifting with satisfactory results. However, poor wound healing, friable skin, and keloid formation can happen [2], and the extrusion of calcium through the healing scars can occur [1,8]. Injectable Collagen: There are reports about treating horizontal chin creases with injectable collagen, and the treatment showed temporary improvement for up to a few months [2]. Laser CO_2 Fractional: There are reports about resurfacing of the skin by using a Fractional CO_2 Laser. After the laser treatment, the reaction of the PXE - affected skin was similar to that of the normal skin. The result after 2 years was an improvement in skin texture, surface irregularities [9]. Side effects that can occur are hyperpigmentation, imflammation of the skin and a recurrence of a local Herpex simplex [2].

However, with the large extent of the skin lesions in our patient, the methods above are almost impossible to perform.

Suggested management of patients with PXE [1]: Eye examination: 6 - 12 monthly check by ophthalmologist. Regular use of Amsler grid by patients to monitor central vision. Cardiology assessment: Yearly check of blood pressure, peripheral pulses, and for heart murmurs. If abnormal findings, refer to cardiologist for further investigations. Laboratory tests: In children low thresholdor in adults 6 - 12 monthly. Blood count, ferritin, serum lipids, urinalysis. Medicaments: Avoidance of non - steroidal anti - inflammatory analgesics and Warfarin. Selective use of Aspirin for prevention of thromboembolic events in high risk patients. Avoidance of oestrogens, e.g., oral contraceptive pill, HRT. Diet: Avoid high cholesterol. Moderate calcium intake. Lifestyle: Regular exercise but avoid contact sports and straining. Weight control. Avoidance of smoking.

IV. CONCLUSION

Pseudoxanthoma Elasticum is a rare disease, so the orientation and recognition of PXE is extremely important because it is associated with the risk of blindness and peripheral vascular compromise. The faster the detection and setting of diagnosis are made, the more extreme the preventive measures and the surveillance to prevent and control the progression of the disease are applied.

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