Eruptive xanthoma (EX), localized deposition of lipids in the dermis, is usually caused by extreme hypertriglyceridaemia associated with underlying metabolic-related disorders (1). Early recognition of EX can help avoid serious complications, such as acute pancreatitis and cardiovascular disease. However, due to misdiagnosis or delayed diagnosis some patients with EX do not receive effective therapies. We report here a case of EX, an unusual manifestation presenting as the first sign of undiagnosed hyperlipoproteinaemia and diabetes secondary to Klinefelter syndrome (KS).

CASE REPORT

A 30-year-old man presented to our department with a non-pruritic, tender rash on the extensor surfaces of his extremities for 6 months. The lesions began on his elbows as small red bumps that increased in size and turned yellow over time. On examination, multiple yellowish, waxy, dome-shaped papules or nodules were noted, mainly involving the elbows and knees, with a diameter of 3–10 mm (Fig. 1a, b).

A skin biopsy of a papule on his right elbow showed infiltration of lipid-laden macrophages with foamy and vacuolated cytoplasm within the dermis (Fig. 1c, d). A lipid profile was conducted with extremely high levels of triglyceride (TG; 7,333.4 mg/dl; normal <149.0 mg/dl), cholesterol (954.5 mg/dl; normal <219.0 mg/dl), low-density lipoprotein (LDL; 290.7 mg/dl; normal <140.0 mg/dl), high-density lipoprotein (HDL; 126.8 mg/dl; normal <60.0 mg/dl) and a slightly decreased level of apolipoprotein B (0.5 g/l; normal 0.6–1.4 g/l). In addition, high levels of blood glucose (25.8 mmol/l; normal 3.9–11.0 mmol/l) and haemoglobin A1c (13.1%; normal 4.3–6.0%) were found. A diagnosis of EX associated with severe hyperlipoproteinaemia and hyperglycaemia was considered, and the patient was referred to the department of endocrinology for further treatment.

Consultation with an endocrinologist revealed that the patient had lost 18 kg in weight and had had polydipsia for 2 months. The patient reported that they had no history of eating disorders or drug abuse and no family history of metabolic diseases or tumours. An oral glucose tolerance test (OGTT) and C peptide release assay were conducted, with a result of hyperglycaemia and delayed peak C peptide level. An endocrine diagnosis of hyperlipoproteinaemia and type 2 diabetes mellitus (T2DM) was considered, and fenofibrate and insulin were prescribed. After 2 weeks, the levels of TG (537.8 mg/dl), TC (227.3 mg/dl), HDL-C (34.0 mg/dl), LDL-C (153.0 mg/dl) and blood glucose decreased.

The patient also reported that he had been unable to ejaculate and had not had morning erections for almost 4 years. He denied any history of testicular injuries or exposure to radiation, cryptorchidism, or varicocele. Physical examination revealed very small testes with a volume of approximately 4 ml, sparse pubic hair, and a small penis, approximately 4 cm in length (Tanner stage: B1G4P4). Further endocrinological evaluations were performed.

He had elevated levels of luteinising hormone (LH; 18.1 mIU/ml; normal 1.2–8.6 IU/l), follicle stimulating hormone (FSH; 23.1 IU/l; normal 1.3–19.3 IU/l) and decreased level of testosterone (1.3 ng/ml; normal 1.8–7.8 ng/ml), suggesting hypergonadotropic hypogonadism. In addition, his testosterone level decreased following human chorionic gonadotropin (hCG) stimulation, and LH and FSH levels increased following stimulation with gonadotropin-releasing hormone agonist. Ultrasound examination confirmed the small size of the testes (Fig. 1e, f). Adrenal computed tomography (CT) and pituitary magnetic resonance imaging (MRI) scanning were normal. Chromosome karyotype analysis revealed 47, XXY karyotype (Fig. 1g). Therefore, a final diagnosis of KS was made, and testosterone undecanoate replacement therapy was added. Two months later, levels of serum testosterone, LH, FSH, blood glucose, and lipid returned to normal, and the EX lesions gradually resolved.

DISCUSSION

EX is clinically characterized by multiple, yellowish, waxy papules and nodules that arise primarily on the extensor surfaces of extremities and back. This skin condition could be an early clue to systemic diseases. It is usually caused by extreme hypertriglyceridaemia, a condition associated with several underlying disorders, including diabetes mellitus, hypothyroidism, nephrotic syndrome, liver cirrhosis, and excess ethanol ingestion, as well as certain medications, such as retinoids and oestrogen (1). T2DM was a comorbid condition of the current patient, one of the most commonly reported underlying causes of EX. T2DM is a complex and multifaceted disease developed in middle-aged patients with obesity and a family history of diabetes (2), in contrast to the current patient who was a young man with a normal body mass index (BMI) (21.4 kg/cm²) and no related family history of diabetes. It has been reported that T2DM can be caused by various factors, including pancreatic diseases, trauma, drugs, endocrinopathies, infection with human immunodeficiency virus, and several genetic syndromes, such as Down syndrome, KS, and Turner syndrome. In the current case, the patient had small testes, no ejaculation, and hypergonadotropic hypogonadism, finally leading to a diagnosis of KS.

KS is a group of chromosomal disorders resulting from the presence of 1 or more extra X chromosomes, characterized by hyalization of the seminiferous tubules, azoospermia, infertility, and hypergonadotropic hypogonadism (3). It is the most common sexual chromosomal abnormality in males, affecting approximately 1 in every 650 newborns. Approximately 80–90% of...
cases of KS are classic form with a 47, XXY karyotype, whereas various forms of mosaicism (47, XXY/46, XY), higher-grade X chromosome aneuploidies (45, XXXY or 48, XXYY), or a structurally abnormal X chromosome (X isochromosome) may be detected in the remaining 10–20% of cases (4).

KS manifests itself in a variety of phenotypes, and the classic form is characterized by tall, slender stature with narrow shoulders, long arms and legs, small testes, and infertility (3). Nevertheless, according to data from Denmark, the lifetime diagnostic rate in affected patients was estimated to be as low as 25% (4). Many individuals with KS may present with subtle clinical findings, complicating the diagnosis, such as motor, cognitive, and behavioural dysfunction, tumours, vascular disease, and metabolic diseases (5). Epidemiological studies have found that the prevalence of T2DM in KS ranges from 15% to 50%. Although the pathophysiological correlation has not been well understood, hypogonadism and the supernumerary of the X chromosome may explain the vicious cycle of insulin resistance, body composition, and metabolic disorders (6, 7). There is a higher incidence of diabetes in individuals with atypical forms of KS, such as the 48, XXXY, and the 49, XXXXY karyotype, suggesting that a gene dosage effect of the X chromosome may contribute to insulin resistance. In addition, the number of CAG repeats in the androgen receptor, located on the X chromosome, is also associated with the metabolic phenotype of KS (8).

Some skin diseases might be clues to remind us to consider KS as a possible diagnosis, including certain X-linked genodermatoses, such as incontinentia pigmen-
ti and focal dermal hypoplasia, leg ulcer in young men, male breast cancer, and gynaecomastia (9). However,
only 1 EX patient with KS has been reported previously, which presents a new challenge for physicians (10). In patients with EX, it is recommended that the Four D’s (Diet, Drugs, Disorders of metabolism, and Diseases) of secondary hypertriglyceridaemia should be evaluated in order to provide early diagnosis and target treatment (11).

We report here an uncommon, but significant, skin manifestation of KS, reminding physicians that EX may be a sign of an uncontrolled metabolic condition, and X-linked disorders, such as KS and Turner syndrome, may be the primary factor behind these metabolic diseases.

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