—Case Reports—

Refractory Leg Ulcers Associated with Klinefelter Syndrome

Yuto Yabuno[1], Mamiko Tosa[1], Itaru Iwakiri[1], Shunichi Nomoto[1], Mayuko Kaneko[1], Kousuke Kuwahara[1], Hiko Hyakusoku[2] and Masahiro Murakami[1]

[1]Department of Plastic and Reconstructive Surgery, Nippon Medical School Musashi Kosugi Hospital
[2]Department of Plastic, Reconstructive and Aesthetic Surgery, Nippon Medical School

We present a man with refractory leg ulcers, bilateral varicosis of the lower extremities, and Buerger disease. Autoimmune work-up was negative. However, chromosome analysis showed Klinefelter syndrome (48 XXY). Ulcerative lesions of the lower extremities are a complication of Klinefelter syndrome. To date, the pathogenesis of ulcers in Klinefelter syndrome has not been clarified, but several factors, such as abnormalities of fibrinolysis and prothrombotic states, might be involved. Our present case emphasizes the importance of considering Klinefelter syndrome in the differential diagnosis of a male patient with nonhealing ulcers of the lower extremities. (J Nippon Med Sch 2015; 82: 64–67)

Key words: Klinefelter syndrome, refractory leg ulcer, XXY, fibrinolysis, prothrombotic state

Introduction

Klinefelter syndrome is a rare disorder of the sex chromosomes. Patients with this syndrome have at least one extra X chromosome in addition to the normal male karyotype of 46, XY[1]. Among the clinical manifestations of dermatological interest, leg ulcers occur in 13% of cases of Klinefelter syndrome[2]. We describe a patient with Klinefelter syndrome who had had refractory leg ulcers for 19 years but did not show spontaneous aggregability of platelets or elevated activity of plasminogen activator inhibitor type 1 (PAI-1), but did show a low testosterone level and elevated levels of follicle-stimulating hormone and luteinizing hormone.

Case

A 44-year-old unmarried man was admitted to our hospital for refractory bilateral leg ulcers, which had been present for nearly 18 years. His job as a chef at a sushi restaurant involved prolonged hours of standing. Since the age of 26 years he had received treatment in the department of vascular surgery for painful bilateral leg ulcers (**Fig. 1**), for which Buerger disease had been diagnosed, and bilateral varicose veins of the lower extremities. The patient was uncooperative toward treatment and repeatedly admitted to the hospital: 9 times in total over a period of 18 years. However, they had believed that these diseases was the cause of the ulcers, treatment for these diseases made no remarkable change of ulcers, therefore the patient was referred to our department.

On admission, physical examination revealed obesity (height: 170.0 cm, weight: 98 kg, body-mass index, 33.9 kg/m^2) with long legs and eunuchoid body proportions (**Fig. 2**). Body hair was sparse. However, gynecomastia was absent, and testes and penis were of normal size. An 8×5-cm ulcer was observed over the dorsum of the right foot and ankle. The ulcer was covered with hard, yellow necrotic tissue and the extensor hallusis longus muscle tendon was exposed at the ulcer of the tendon (**Fig. 3**). There were also multiple ulcers, hyperpigmentation lesions and a tendency towards skin atrophy due to stasis dermatitis on both legs, similarly covered with necrotic tissue. The dorsalis pedis and posterior tibial pulses were palpable bilaterally in the legs. Venous Doppler ultrasonography of the leg showed dilated veins with reflux and an incompetent perforating vein with no aneurysms just under the ulcer of the right foot and ankle. Pathological examination of this ulcer showed no malignancy.

Laboratory studies revealed no abnormalities of blood biochemistry, the immune system, or fibrinolytic variables, such as prothrombin time, partial thromboplastin time, and serum levels of fibrinogen and plasminogen. No spontaneous aggregation of platelets was observed,

Correspondence to Yuto Yabuno, MD, Department of Aesthetic and Plastic Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8602, Japan
E-mail: yabuno@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

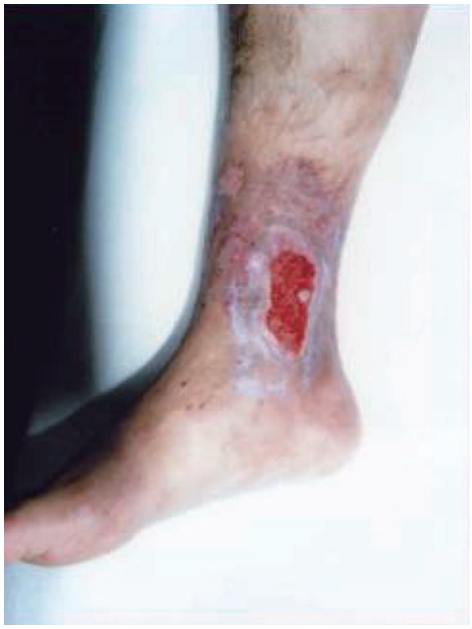

Fig. 1 Right leg ulcer (5×2 cm) at medial malleolus and pigmentation around the ulcer seen at the age of 26 years.

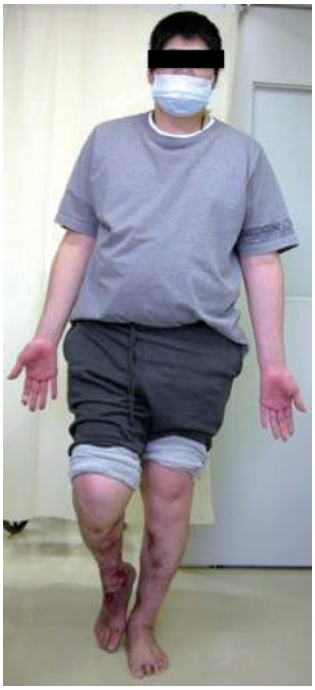

Fig. 2 Patient's body showing eunuchoid proportions, obesity, and long extremities.

and the adenosine diphosphate threshold concentration and the activity of PAI-1 were also normal. Hormonal examinations revealed a low serum testosterone level (0.28 ng/dL, normal range for men: 1.31–8.71 ng/dL) and elevated levels of follicle-stimulating hormone (43.2 mIU/mL; normal range: 2.0–8.14 mIU/mL) and luteinizing

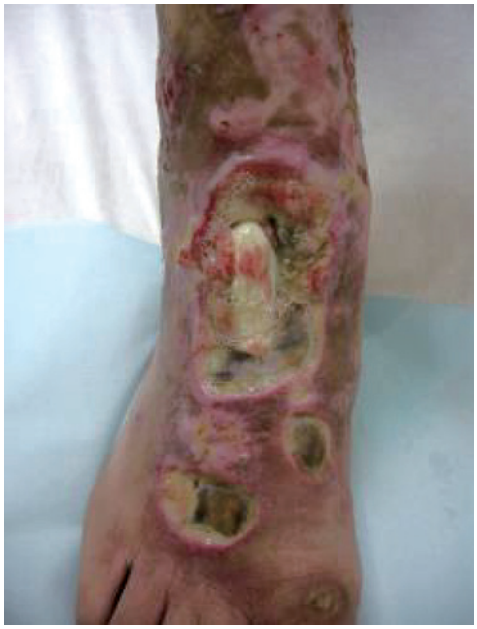

Fig. 3 Dorsum of the right foot at the age of 44 years.

hormone (16.8 mIU/mL; normal range: 0.8–5.7 mIU/mL).

Because of these abnormalities of hormone levels and body proportion, chromosome analysis with Giemsa banding was performed. A 47,XXY/46,XY mosaic karyotype was found, and a diagnosis of Klinefelter syndrome was made.

We immediately hospitalized the patient and started androgen replacement therapy, with monthly injections of 250 mg of testosterone enanthate for 2 months. Some ulcers showed improvement, but therapy could not be continued because of the patient's emotional instability such as becoming short temper.

The persistent ulcers had been treated with ointments, surgical debridement, split-thickness skin grafts, and advanced biointeractive skin dressings but had not healed completely. On pathological examination, organized thrombi and evidence of recanalization were noted (**Fig. 4**). Bacterial cultures of the ulcers obtained on admission yielded *Pseudomonas aeruginosa,* but cultures obtained 8 days later were negative.

We performed a negative pressure wound treatment for 1 month. As a result of this treatment, the ulcers did not heal completely but were considerably improved. However, we complied with the patient's request for discharge, and he was directed to the outpatient clinic for follow-up after 10 months admission.

At discharge, we had told the patient the importance of continuous treatment. As a result, the patient finally recognized the importance of treatment and, more than 1 year after initial visit, the ulcers had healed completely

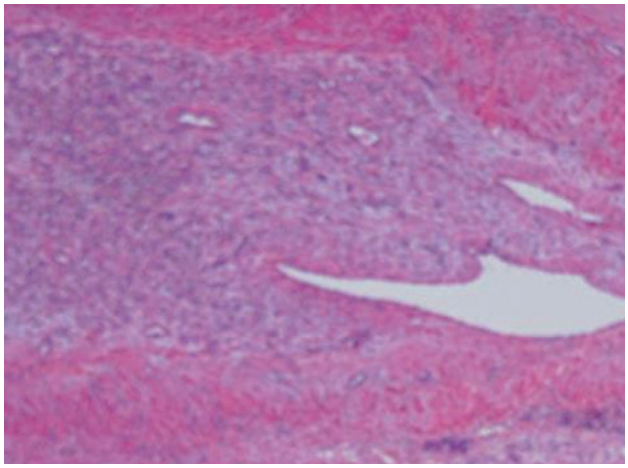

Fig. 4 Histologic section showing an organized thrombus and recanalization in a small artery

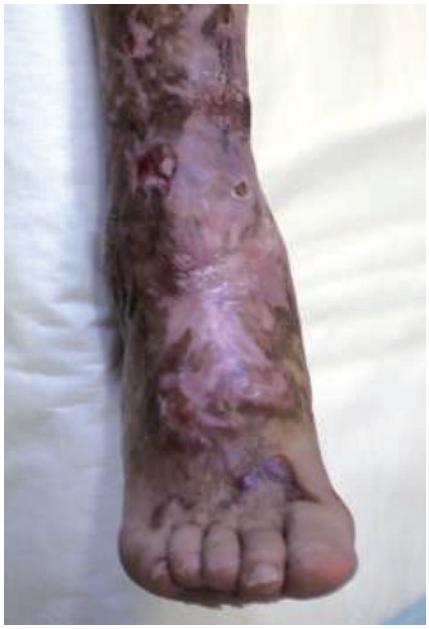

Fig. 5 Dorsum of right foot at the age of 46 years, 13 months after initial visit.

(**Fig. 5**).

Discussion

Klinefelter syndrome was first reported by Klinefelter, et al.[1] in 1942, is present at approximately 1 in 500 to 1,000 male births[3]. The characteristics include testicular atrophy, azoospermia, infertility, elevated urinary levels of gonadotropins, behavioral disorders, and mild intellectual disability. The physical findings include a eunuchoid body habitus, long lower extremities, gynecomastia, and sparse body hair.

The prevalence of leg ulcers in persons with Klinefelter syndrome is 6% to 13%[2], which is 3 to 30 times higher than that in the general population. Such leg ulcers are often refractory to treatment. Furthermore, determining that the ulcers are caused by Klinefelter syndrome often takes a long time.

The pathogenesis of the leg ulcer is complicated, although a combination of the following factors is thought to be involved: 1) body proportion (venous incompetence caused by increased venous pressure associated with the long legs); 2) hormonal abnormality (inhibition of fibrinolysis caused by low testosterone levels or imbalance of the estrogen to androgen ratio)[4]; 3) abnormal coagulation and fibrinolytic systems (tendency toward thrombosis caused by increased platelet aggregation[5], and microemboli caused by impairment of the fibrinolytic system associated with an increased activity of PAI-1[6]); 4) hypercoagulation caused by genetic defects of coagulation and fibrinolysis factors[7]; 5) comorbid diabetes mellitus and autoimmune diseases, including systemic lupus erythematosus and anti-phospholipid antibody syndrome; and 6) congenital anomalies (partial defects of the venous endothelial cells and defects of the venous valves)[8]. Of these factors, abnormal functioning of the fibrinolytic system is most closely associated with hypogonadism; especially in patients with Klinefelter syndrome, the elevated PAI-1 activity levels are believed to be caused by the low levels of testosterone, not by the genetic defect itself. Although many reports on leg ulcers in patients with Klinefelter syndrome have described elevated levels of PAI-1, there are also some exceptions, such as the present patient. Reduced levels of testosterone may cause estrogen dominance, resulting in the development of comorbid autoimmune diseases. The ulcers of the present patient had long been thought by the department of vascular surgery to have been caused by Buerger disease or varicose veins of the lower extremities. However, because the ulcers showed no improvement despite years of the treatment, the patient was referred to our department. Because of the patient's body proportions we suspected Klinefelter syndrome, the presence of which was confirmed by chromosomal analysis. The patient did not have any significant abnormalities of the coagulation or fibrinolytic systems but did have abnormalities of hormonal balance, varicose veins with hyperpigmentation, and a tendency towards skin atrophy due to stasis dermatitis. With these features, a final diagnosis of venous stasis ulcers associated with Klinefelter syndrome was made. The patient's job, which involved prolonged hours of standing, may have contributed to the worsening of the venous stasis leg ulcers. The patient's poor understanding

of the disease and other general issues could also be expected to have contributed to the refractory ulcers. This notion was supported by the numerous hospital admissions (9 over 18 years), the improvement of the ulcers during hospitalization, and their worsening after discharge, possibly because of the patient's unwillingness to visit the outpatient clinic regularly or failure to properly care for the ulcers at home. Some patients with Klinefelter syndrome are believed to have mild intellectual disability, with lower verbal intelligence quotient scores than performance scores. Deficits in the language understanding domain due to delays in speech and language abilities is a feature of Klinefelter syndrome[9]. This imbalance may cause unstable cognitive competence. In the present patient, the additional "negative" personality specific to the patient seemed to be the cause of the extremely poor compliance with the treatment.

In Japan, 51 cases, including the present case, of leg ulcers in patients with Klinefelter syndrome have been reported. There is no established therapy for leg ulcer, but some of the reports[10] have suggested that administration of testosterone encourages healing; however, the treatment developed some problems, such as short temper, and the patient wished to stop further administration of testosterone. We also could heal the leg ulcer to resume the small amount of testosterone administration in the future.

In conclusion, in patients with refractory, recurrent leg ulcers with underlying stasis dermatitis, Klinefelter syndrome should be considered in the differential diagnosis. In patients with Klinefelter syndrome it is important to broaden treatment options, such as androgen replacement therapy and dealing with lack of consciousness about the ulcers.

Conflict of Interest: The authors have no conflicts to disclose.

References

1. Klinefelter HF, Reinfenstein EC, Albright F: Syndrome characterized by gynecomastia, aspermatogesis without aleydigism, and increased excretion of follicle-stimulating hormone. J Clin Endocr 1942; 2: 615–627.
2. Campbell WA, Newton MS, Price WH: Hypostatic leg ulceration and Klinefelter's syndrome. J Ment Defic Res 1980; 24: 115–117.
3. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E: Kleinefelter syndrome. Lancet 2004; 364: 273–283.
4. Caron P, Bennet A, Camare R, Louvet JP, Boner B, Sié P: Plasminogen activator inhibitor in plasma is related to testosterone in men. Metabolism 1989; 38: 1010–1015.
5. Shanmugam VK, Tsagaris KC, Attinger CE: Leg ulcer associated with Klinefelter's syndrome: a case report and review of literature. Int Wound J 2012; 9: 104–107.
6. Veraart JC, Hamulyak K, Neumann HA: Leg ulcers and Klinefelter's syndrome. Arch Dermatol 1995; 131: 958–959.
7. Lapecorella M, Marino R, De Pergola G, Scaraggi FA, Speciale V, De Mitrio V: Severe venous thromboembolism in young man with Klinefelter's syndrome and heterozyosis for both G20210A prothrombin and factor V leiden mutations. Blood Coagul Fibrinolysis 2003; 14: 95–98.
8. Campbell WA, Price WH: Venous thromboembolic disease in Klinefelter's syndrome. Clin Genet 1981; 19: 275–280.
9. Theilgaard A: Cognitive style and gender role in persons with sex chromosome aberrations. Dan Med Bull 1972; 19: 276–286.
10. Goto Y, Uhara H, Murata H, et al.: Leg ulcers associated with positive lupus anticoagulant in two cases of Klinfelter's syndrome. Acta Derm Venerol 2011; 91: 90–91.

(Received, May 21, 2014)
(Accepted, September 22, 2014)