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Case Report

Surgical correction of kyphotic deformity in a patient with Proteus syndrome

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Abstract

BACKGROUND CONTEXT: Proteus syndrome (PS) is an extremely rare congenital disorder causing asymmetric overgrowth of different tissues. The etiology remains unclear. Limb deformities are common and often necessitate amputations. Only a few cases associated with spinal deformities have been described.

PURPOSE: The aim was to report a rare case of PS associated with spinal deformity and its surgical management.

STUDY DESIGN: A case of young boy with PS causing vertebral hypertrophy and kyphoscoliotic deformity, which was surgically corrected, is presented.

METHODS: The patient was assessed clinically and with whole spine plain radiographs, computed tomography, and magnetic resonance imaging. Surgical correction was performed.

RESULTS: Satisfactory correction of the deformity was achieved by posterior spinal fusion with instrumentation from T4–L5, five Ponte osteotomies T8–L1, and an L2 pedicle subtraction osteotomy. The kyphosis was corrected from 87° to 55°; there was improvement in all spinopelvic parameters. One year after surgery, there was maintenance of the deformity correction with no deterioration of the sagittal balance, and the patient was free of pain and had no loss of neurologic function.

CONCLUSIONS: Proteus syndrome can be associated with spinal stenosis and deformity. Although the syndrome can be progressive in nature, the symptomatic spinal pathology should be treated appropriately.

Keywords: Proteus syndrome; Kyphosis; Spinal instrumentation; Spinal deformity; Overgrowth; Spinal osteotomy

Introduction

A patient with the signs of Proteus syndrome (PS) was first described in 1979 [1]. The syndrome was assigned its name several years later [2] after the Greek god of the sea, Proteus, who could change his form at will to avoid capture. The etiology remains unclear. However, there is evidence that it occurs as a result of mutation of the oncogene *AKT1*. This mutation is typically lethal, except in the setting of mosaicism. This gene encodes the AKT1 kinase, an enzyme known to mediate processes such as cell proliferation and apoptosis [3]. The syndrome is extremely rare, and its diagnosis is still controversial because of high interpatient variation and overlap with other asymmetric overgrowth syndromes.

Clinical presentation is typically asymmetric partial gigantism and hemihypertrophy, which can affect any body tissue; however, bone connective tissue and fat are the most commonly involved. Clinical findings include macrodactyly, subcutaneous tumors, plantar or palmar hyperplasia, cranial exostosis, kyphoscoliosis secondary to vertebral abnormalities, and other skeletal anomalies [4]. The clinical

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course is usually rapidly progressive in childhood in which the affected bones can become unrecognizably distorted. The progression may, however, slow or stabilize during early adolescence. The patients are prothrombotic, often leading to premature death due to deep vein thrombosis and pulmonary embolism.

We present a young male patient with PS causing vertebral hypertrophy and resultant kyphoscoliosis, which was surgically corrected.

Case report

A 12-year-old boy attended the spinal outpatient clinic with back pain and progressive kyphotic deformity. He was diagnosed with the PS at the age of 5 and a half years. There was no family history of the condition. His visual analog scale pain score was 6 of 10. He stood with a flexed left knee and hip and a plantigrade foot. This posture compensated for his left leg hemihypertrophy and balanced his pelvis. His shoulders were level. He had a right rib prominence and thoracic kyphosis, which were not correctable. He had mild waist asymmetry, trunk shifting, and listing to the right. He had a flexion contracture of the left hip and knee (Fig. 1). There was no neurologic deficit, and his abdominal reflexes were symmetrical. There was no clinical evidence of a deep vein thrombosis in either leg.

Whole-spine radiographs demonstrated a global kyphotic deformity of 63° (T4–L3) and a long C-shaped scoliosis measuring 25° (T2–L3). A computed tomography scan of the spine revealed severe dystrophic changes: apart from C1–C4, all the vertebral bodies showed marked hyperplasia of the posterior elements. Incomplete segmentation of the vertebral bodies and posterior arches was particularly marked around the cervicothoracic junction. There was also severe canal stenosis in the thoracic and lumbar region owing to the bony overgrowth of the posterior elements, especially in T11–L1 and L4–S1 levels. The computed tomography scan also showed long narrow thorax (Figs. 2–4). A magnetic resonance image of the spine revealed syringomyelia at C6–C7 level (Figs. 5 and 6). He was followed up on a regular basis with a radiograph of his whole spine.

The surgical correction was performed 2 years after the initial presentation (at the age of 14 years) when the kyphotic deformity had progressed to 87° (Fig. 7) and the scoliosis to 36°. There was now a clinical imbalance of shoulders and pelvis, his visual analog scale pain score had increased to 7 to 9 of 10, and he was complaining of right L5 radiculopathy. On examination, there was no objective deterioration in his neurologic function compared with the initial presentation 2 years previously. The preoperative lumbar lordosis was 23°, and the spinopelvic parameters were sacral slope, 27°; pelvic incidence, 56°; pelvic tilt, 29°; and sagittal vertical axis, 140 mm. He was now Risser Grade 3 to 4. His weight was 61.6 kg and he was 172.5 cm in height, equating to a body mass index of 20.5.

Procedure

A posterior correction of the deformity was performed under general anesthesia with dual-modality spinal cord monitoring. Intermittent calf pneumatic compression devices were used for perioperative thromboembolic prophylaxis. The patient was positioned prone on Montreal mattress ensuring that the abdomen was hanging free. A subperiosteal exposure of the spine was performed up to the tips of the transverse processes bilaterally. After meticulous hemostasis, five Ponte osteotomies were carried out from T8–L1 [5], and at L4–L5, a discectomy and decompression was performed. The posterior spinal architecture was significantly hypertrophic, but the bone was soft. Bilateral segmental pedicle screws were placed (T4–L5) using a freehand technique [6,7]. A pedicle subtraction osteotomy (PSO) was performed [5] at L2. Temporary rods prevented sudden sagittal translation during the PSO. Definitive contoured rods were first secured to the lumbar region and then to the thoracic spine to close down the osteotomies, correcting and stabilizing the deformity. Morcellized local bone mixed with demineralized bone matrix was used as bone graft after decortication. The total blood loss was 1,170 mL. There was no perioperative bleeding or thromboembolic complications. Chemical thromboembolic prophylaxis was started postoperatively on the day of surgery, with a regime of 20-mg enoxaparin twice daily. Anti–factor Xa assays were performed 4 hours after the third dose, and subsequently, the dose of enoxaparin was increased to 30 mg twice daily, which resulted in factor Xa levels falling within the therapeutic range. He continued on this regime for 3 months after surgery. He was discharged after 18 days, when he was able to move from bed to chair, and he wore a molded thoracolumbosacral orthosis (TLSO) for 3 months.

Outcome, follow-up

The patient was seen at 3 and 12 months after surgery. Radiographs were taken at 3 months; the thoracic kyphosis had been corrected to 55°, the lumbar lordosis to 36°, the scoliosis to 13°, sacral slope to 19°, pelvic tilt to 26°, and sagittal vertical axis to 30 mm (Fig. 8). At 12 months, he was able to walk on his right leg using walking sticks. He is currently on the waiting list for a midthigh amputation of his left leg due to the intractable flexion deformity of his left knee. The surgery resulted in a significant improvement in his back pain, which at 12 months was 1 to 2 of 10, and there remained no neurologic deterioration after surgery (Fig. 9). The whole-spine radiographs, at 12 months, showed a satisfactory correction of the deformity, with maintenance of the correction over time.

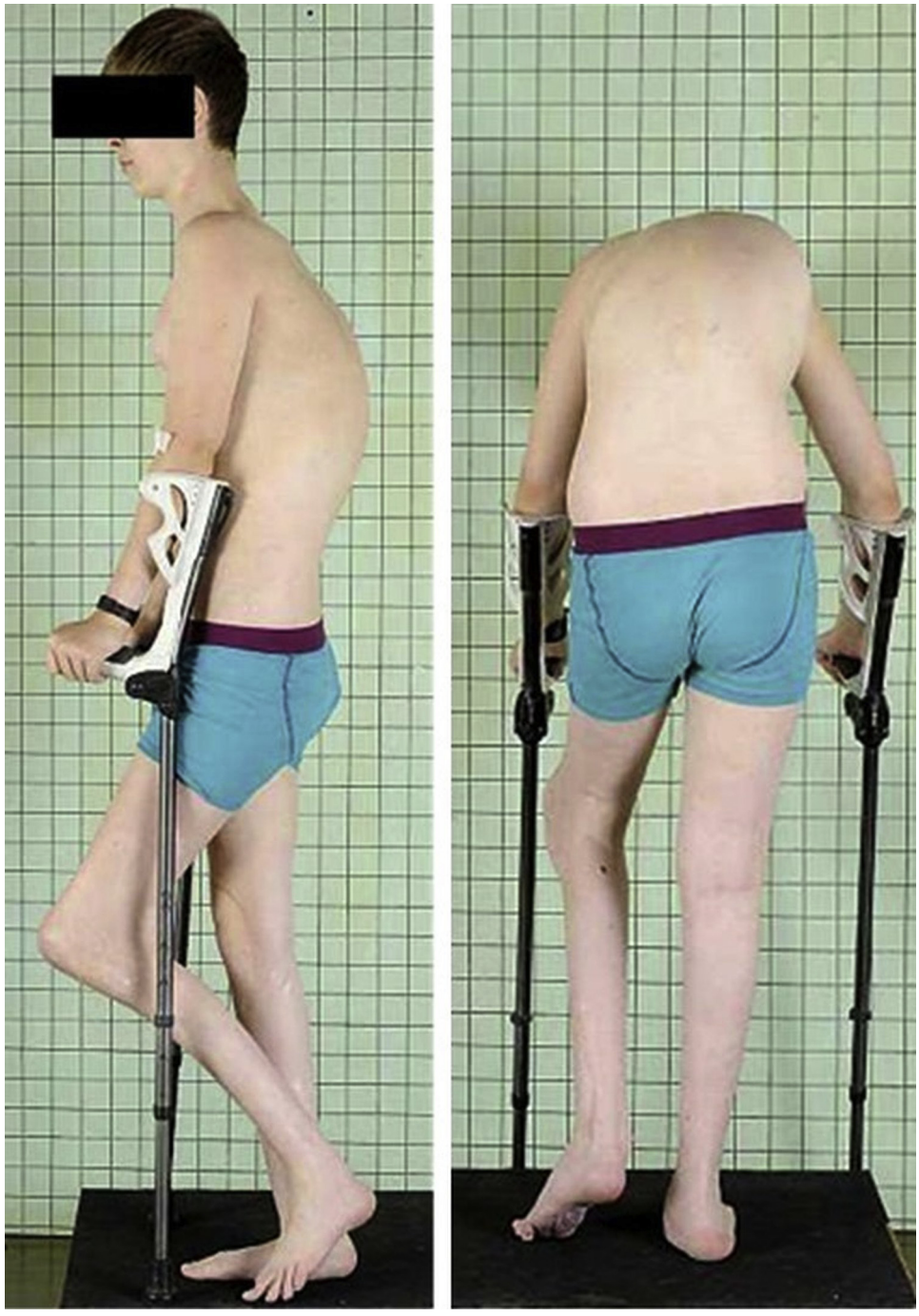

Fig. 1. Preoperative photographs showing severe thoracic deformity and flexion deformity of the left knee.

Discussion

The diagnosis of PS is based on the clinical and radiological evaluation. The general diagnostic criteria of PS are a mosaic distribution of the phenotype, sporadic manifestation, and progressive behavior of the disease. If a patient has all these general attributes, the specific criteria should be assessed. These should include the single Category A sign (cerebriform connective tissue nevus), two signs from Category B (linear epidermal nevus, disproportionate overgrowth, and specific tumors before the second decade of life), or three signs from Category C (dysregulated adipose tissue, vascular malformations, lung cysts, and facial phenotype) [8]. Dysregulation of fatty tissue includes both hypertrophy and atrophy. The intelligence and life expectancy are normal in most cases [9]. Proteus syndrome appears to be associated with a number of tumors, especially parotid adenomas and ovarian cystadenomas. However, there is little evidence that early detection of tumors in these patients can

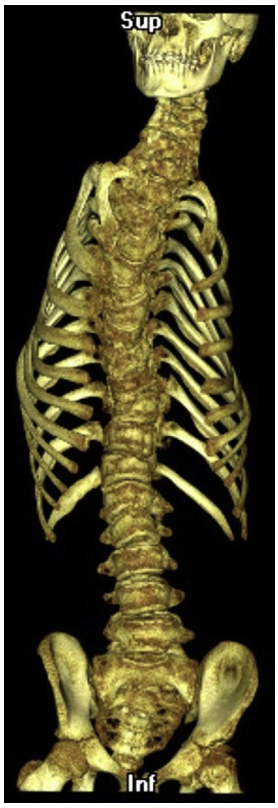

Fig. 2. Three-dimensional reconstruction of whole-spine CT.

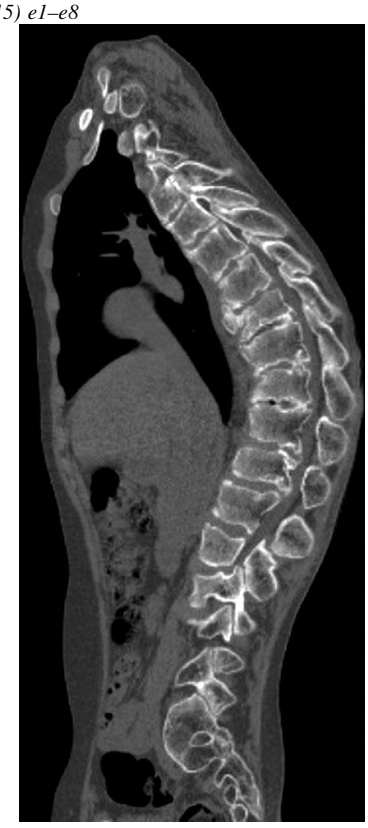

Fig. 4. Sagittal whole-spine CT reconstruction showing dystrophic changes of the vertebrae.

improve prognosis. Routine imaging surveillance for tumors is therefore not recommended. The rate of premature death is around 20%, and it has been clearly demonstrated that one of the most common causes of death for PS patients is thromboembolic disease, even in young children. Perioperative anticoagulant prophylaxis should therefore be strongly recommended [8]. Vascular malformations and skin manifestations (verrucous epidermal nevus) with asymmetric overgrowth are typical for PS but also encompasses other disorders, which must be excluded when making this diagnosis. This is especially true for Klippel-Trenaunay-Weber syndrome and neurofibromatosis Type 1. Soft-tissue hypertrophy in Klippel-Trenaunay-Weber syndrome is present at birth and is usually severe, while bone involvement is absent. Neurofibromatosis Type 1 is distinguished from PS by the presence of the triad of café-au-lait spots, Lisch nodules, and axillary freckling [4,8].

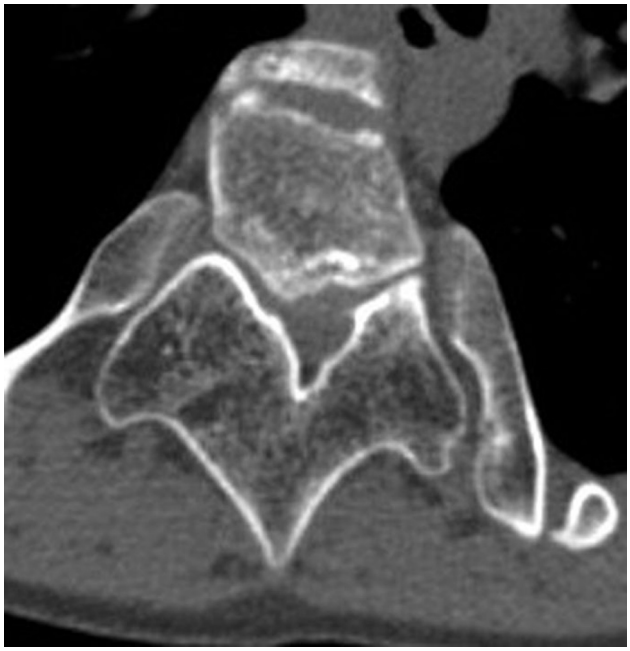

Fig. 3. Hypertrophy of posterior arch of T5 vertebra on axial CT scan.

Our patient met all the general criteria. Moreover, he underwent amputation of his great toe on the left foot because of connective tissue nevus (Category A), and he suffers also from disproportionate overgrowth (Category B).

It has been suggested that regular follow-up, including serial magnetic resonance imaging, is indicated in children with PS and scoliosis because of risk of spinal cord compression. It can arise from vertebral abnormalities, kyphoscoliotic deformity, or tumor encroachment [10]. Yamamoto et al. [11] described a case of PS patient with severe spinal canal stenosis, scoliosis, cervical kyphosis, and thoracic deformity with airway obstruction because of asymmetric overgrowth of vertebrae and ribs associated with a tethered cord, lipomas, strawberry hemangioma, flat nasal bridge, and bilateral hypoplasty of the first

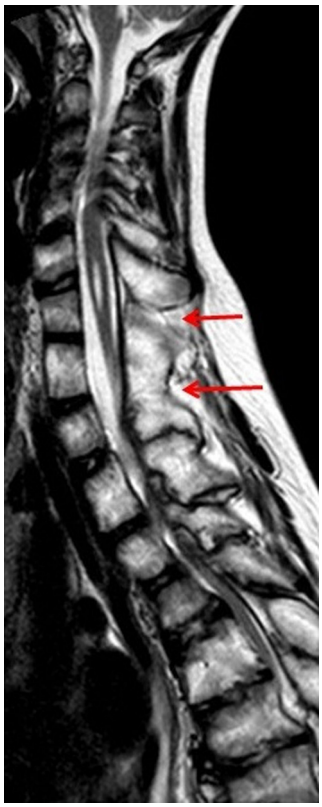

Fig. 5. Sagittal T2-weighted MRI scan showing syrinx in C6–C7 level and incomplete segmentation of the posterior vertebral elements C6–T1 (arrows).

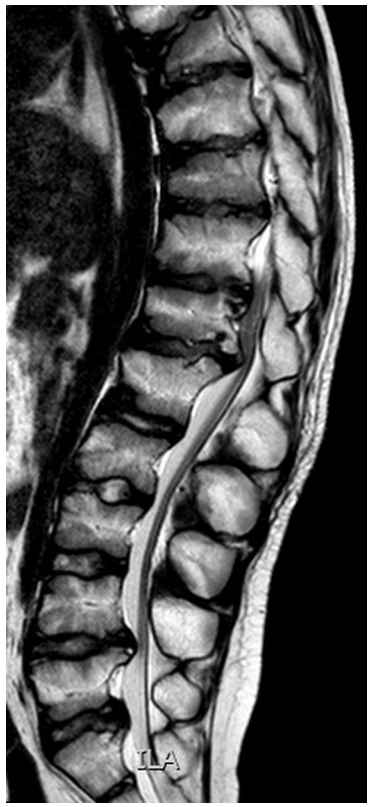

Fig. 6. Sagittal T2-weighted MRI scan showing severe dystrophic changes with posterior osteophytes in T12–L1 and L4–L5 levels.

metatarsal bones with hyperplasty of soft tissue. Sugita et al. reported a case of young girl with PS presenting with progressive fusion and an enlargement of the cervical vertebrae. Her cervical deformity gradually progressed with age, and the abnormal bony protrusion into the spinal canal caused myelopathy. They resected the affected vertebrae to decompress the spinal cord and performed combined anterior-posterior spinal fusion [12]. Takebayashi et al. described a PS patient who underwent corrective scoliosis surgery. Computed tomography showed asymmetric appearance of lumbar spine, hypertrophy of only the right facet joints and right pedicles at L1–L4, which accorded with the right-side hemihypertrophy of the patient's extremities [13]. Yazar et al. [9] reported unsuccessful correction of thoracolumbar scoliosis in a PS patient, which was probably due to the overgrowth potential of the tissues.

The operative indications in our patient were progressive kyphoscoliotic deformity and increasing back pain. The Risser Grade was 3 to 4, but a decision was made to perform a definitive fusion because of his gigantism, the nature of deformity, which is frequently progressive, and the number of osteotomies required to correct the deformity. We performed decompression and discectomy in the L4–L5 level because of his L5 radiculopathy and multilevel decompressions (and Ponte osteotomies) T8–L1 at the most stenotic levels. However, we were aware that progressive overgrowth of the affected vertebrae may result in spinal stenosis at other levels in due course. An L2 PSO was performed using the technique previously described for deformity correction in ankylosing spondylitis patients [5]. Because of the global kyphotic deformity, a long instrumented construct was deemed to be necessary, which included upper- and lower-end vertebrae and stable vertebrae and which spanned all the osteotomies. Therefore, T4 was selected as the upper instrumented vertebrae and L5 as the lower instrumented vertebrae. Because of healthy L5–S1 level and possible risk of sagittal decompensation [14] or pseudoarthrosis [15], we did not incorporate S1 vertebra to the construct. Owing to gigantism, we needed to extend the rods with end-to-end connectors because the longest available rods were too short. The bone was softer than normal bone but strong enough to achieve good grip to the screws. In an attempt to overcome the problems of inadequate correction of the rigid deformity, recurrence, and adding-on phenomenon, we devised a surgical strategy using bilateral segmental pedicle screws at every level to create a long rigid construct and a radical facetectomy at every level, in addition to thoracic and lumbar osteotomies. The osteotomies served not only to correct the deformity, but they were performed in a manner to achieve bone-on-bone apposition after application of the rods and reduction of the deformity. It was hoped that this would facilitate fusion and prevent recurrence.

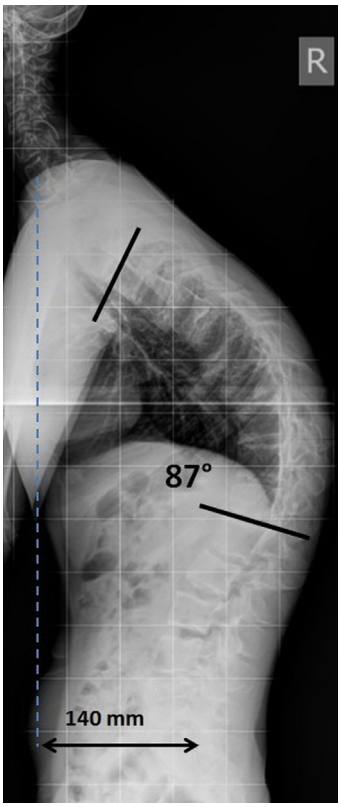

Fig. 7. Preoperative sagittal radiograph showing thoracic hyperkyphosis of 87° and sagittal vertical axis of 140 mm.

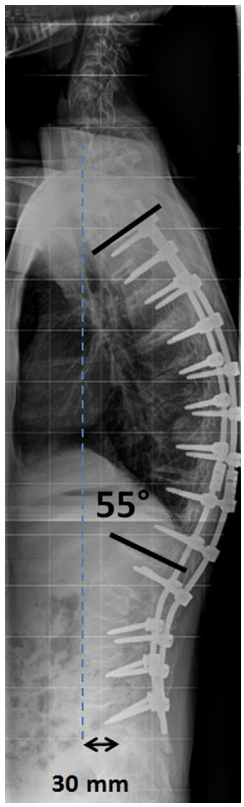

Fig. 8. Postoperative sagittal radiograph showing good correction of kyphotic deformity and SVA.

We routinely take one anteroposterior and lateral radiograph after inserting the screws, and one after final torquing of the instrumentation in deformity surgeries [5,6].

The disease is recognized by the presence of dysplastic or disorganized bone with hyperproliferation of osteoid and abnormally calcified connective tissue [16]. In our case, the hypertrophied posterior elements were slightly softer than normal bone, and this was associated with more blood loss. A significant amount of bone was needed to be removed to perform Ponte and lumbar osteotomies. We used Size 3 and 2 up-cutting rongeurs, which enabled efficient decompressions, limited blood loss, and avoided neurologic injury in such a stenotic canal. Our patient had a nonfunctioning left leg secondary to intractable flexion deformity of the left hip and knee. Although total joint replacement is a possible alternative to amputation, there is no clinical experience with this, and it may present an elevated deep venous thrombosis risk [16]. The leg deformity, therefore, did not change our management of his spinal deformity.

There is no consensus on the effectiveness of different techniques and types of instrumentation used for the correction of thoracic hyperkyphosis. Techniques that are commonly used for deformity correction in patients with the Scheuermann kyphosis [17] or ankylosing spondylitis [5,18,19] include posterior-only and combined anteroposterior spinal fusion with or without posterior osteotomies. Although these techniques can be used in cases of developmental kyphotic or kyphoscoliotic deformities [18,20], our review of the literature failed to find any similar case reports. We performed the surgery by the posterior-only approach by using segmental pedicle screw fixation, which shortens surgical time, minimizes exposure and blood loss, and may reduce postoperative complications [21]. The high risk of thromboembolic complications in PS patients was of particular consideration in our choice of the posterior-only approach. Furthermore, the posterior approach permitted the multilevel osteotomies and decompressions. Generally, osteotomies do not increase the risk of bleeding complications [18,19]. Therefore, we think that this procedure did not worsen the risk-to-benefit ratio of extended thromboembolic prophylaxis. Intraoperatively, we used intermittent pneumatic compression devices, which is one of the primary methods of thromboembolic prophylaxis in spinal surgery [22]. Although the optimal duration of anticoagulant prophylaxis after major orthopedic surgery is uncertain, at least 7 to 10 days of prophylaxis is recommended. However, longer than 4 weeks of prophylaxis may be indicated for discharged patients who remain at high risk for thromboembolism [23]. There are no data about thromboembolic prophylaxis regime in PS patients. Moreover, the mobility of our patient was severely restricted. Therefore, he took 60-mg enoxaparin daily for 3 months after surgery. In addition to providing the patient with comfort and additional relief of pain, the molded TLSO was adapted to sitting and standing exercises. We recommend the use of such a TLSO for 3 months

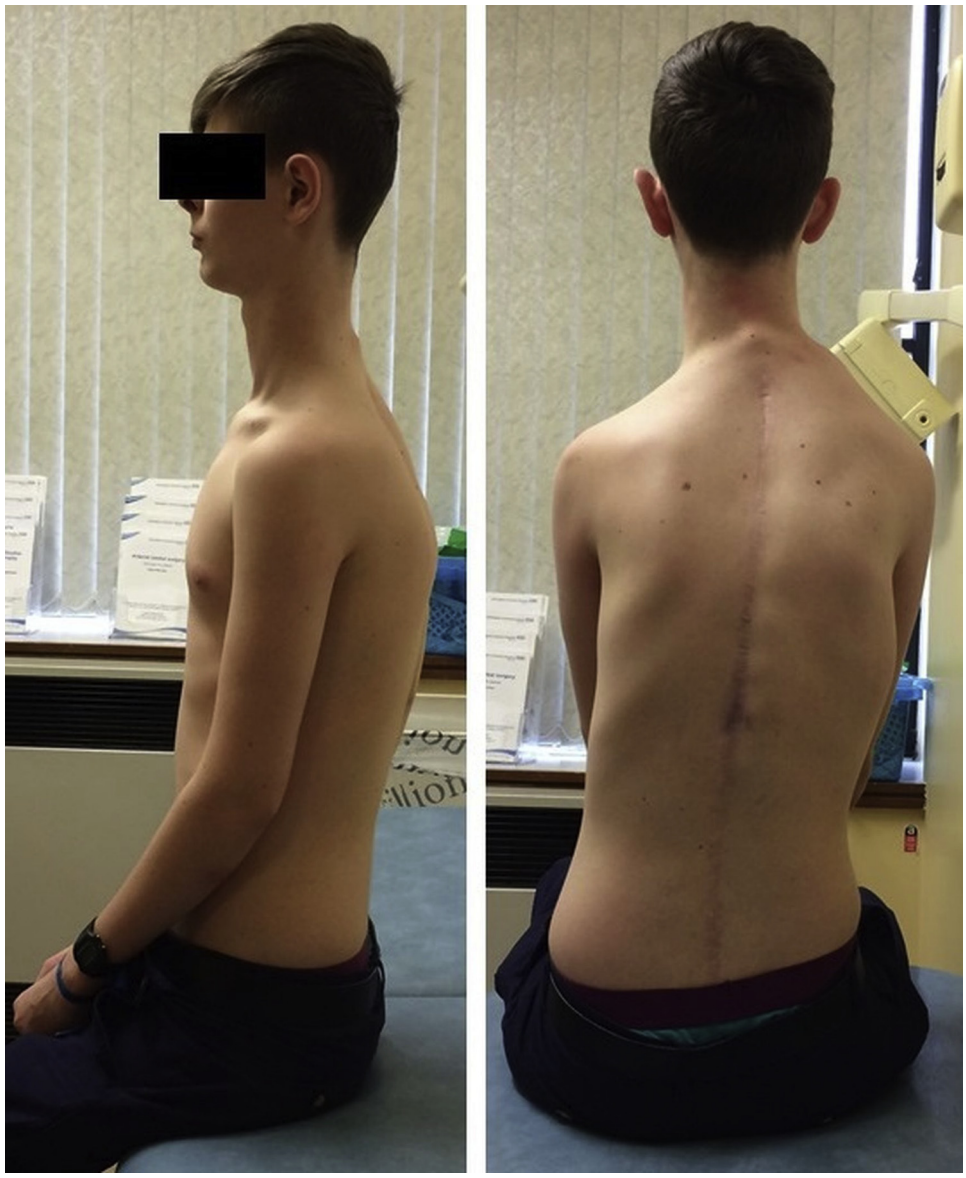

Fig. 9. Postoperative photographs showing good correction of thoracic kyphosis.

postoperatively to protect the instrumentation and osteotomy sites until solid fusion is achieved [5,18].

The surgery was performed to correct the deformity and to prevent its future progression although we were aware of possible general progressive nature of the disease.

Conclusions

Proteus syndrome is very rare. It can be associated with spinal stenosis and deformity. Although the syndrome can be progressive in nature, the symptomatic spinal pathology should be treated adequately.

References

[1] Cohen MM Jr, Hayden PW. A newly recognized hamartomatous syndrome. Birth Defects Orig Artic Ser 1979;15:291–6.

[2] Wiedemann HR, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E. The proteus syndrome. Partial gigantism of the hands and/or feet, nevi, hemihypertrophy, subcutaneous tumors, macrocephaly or other skull anomalies and possible accelerated growth and visceral affections,. Eur J Pediatr 1983;140:5–12.

[3] Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome,. N Engl J Med 2011;365:,611–619.

[4] Kaduthodil MJ, Prasad DS, Lowe AS, Punekar AS, Yeung S, Kay CL. Imaging manifestations in Proteus syndrome: an unusual multisystem developmental disorder. Br J Radiol 2012;85:e793–9.

[5] Arun R, Dabke HV, Mehdian H. Comparison of three types of lumbar osteotomy for ankylosing spondylitis: a case series and evolution of a safe technique for instrumented reduction. Eur Spine J 2011;20:2252–60.

[6] Mehdian H, Elsayed S. Freehand correction of scoliosis in Rett's syndrome. Eur Spine J 2013;22:683–6.

[7] Modi HN, Suh SW, Fernandez H, Yang JH, Song HR. Accuracy and safety of pedicle screw placement in neuromuscular scoliosis with free-hand technique. Eur Spine J 2008;17:1686–96.

[8] Biesecker L. The challenges of Proteus syndrome: diagnosis and management. Eur J Hum Genet 2006;14:1151–7.
[9] Yazar T, Cebesoy O, Basarir K, Karadeniz E. Recalcitrant scoliosis in Proteus syndrome. Acta Orthop Belg 2005;71:372–4.
[10] White NJ, Cochrane DD, Beauchamp R. Paraparesis caused by an angiolipomatous hamartoma in an adolescent with Proteus syndrome and scoliosis. J Neurosurg 2005;103:282–4.
[11] Yamamoto A, Kikuchi Y, Yuzurihara M, Kubota M, O'uchi T. A case of Proteus syndrome with severe spinal canal stenosis, scoliosis, and thoracic deformity associated with tethered cord. Jpn J Radiol 2012;30:336–9.
[12] Sugita S, Chikuda H, Ohya J, Taniguchi Y, Takeshita K, Haga N. Cervical canal stenosis caused by progressive fusion and enlargement of cervical vertebrae with features of Proteus syndrome and Klippel-Feil syndrome. Skeletal Radiol 2013;42:1743–6.
[13] Takebayashi T, Yamashita T, Yokogushi K, Yokozawa H, Cavanaugh JM. Scoliosis in Proteus syndrome: case report. Spine 2001;26:E395–8.
[14] Cho KJ, Suk SI, Park SR, Kim JH, Kang SB, Kim HS. Risk factors of sagittal decompensation after long posterior instrumentation and fusion for degenerative lumbar scoliosis. Spine 2010;35:1595–601.
[15] Edwards CC 2nd, Bridwell KH, Patel A, Rinella AS, Jung Kim Y, Berra AB. Thoracolumbar deformity arthrodesis to L5 in adults: the fate of the L5-S1 disc. Spine 2003;28:2122–31.
[16] Tosi LL, Sapp JC, Allen ES, O'Keefe RJ, Biesecker LG. Assessment and management of the orthopedic and other complications of Proteus syndrome. J Child Orthop 2011;5:319–27.
[17] Tsirikos AI, Jain AK. Scheuermann's kyphosis; current controversies. J Bone Joint Surg Br 2011;93:857–64.
[18] Kim KT, Lee SH, Suk KS, Lee JH, Jeong BO. Outcome of pedicle subtraction osteotomies for fixed sagittal imbalance of multiple etiologies: a retrospective review of 140 patients. Spine 2012;37:1667–75.
[19] Bridwell KH, Lewis SJ, Edwards C, Lenke LG, Iffrig TM, Berra A. Complications and outcomes of pedicle subtraction osteotomies for fixed sagittal imbalance. Spine 2003;28:2093–101.
[20] Imagama S, Tsuji T, Ohara T, Katayama Y, Goto M, Ishiguro N. Surgical treatment for kyphoscoliosis in Cohen syndrome. Nagoya J Med Sci 2013;75:279–86.
[21] Lee SS, Lenke LG, Kuklo TR, Valenté L, Bridwell KH, Sides B. Comparison of Scheuermann kyphosis correction by posterior-only thoracic pedicle screw fixation versus combined anterior/posterior fusion. Spine 2006;31:2316–21.
[22] Glotzbecker MP, Bono CM, Wood KB, Harries MB, et al. Thromboembolic disease in spinal surgery: a systematic review. Spine 2009;34:291–303.
[23] Kearon C. Duration of venous thromboembolism prophylaxis after surgery. Chest 2003;124:386S–92S.