CASE REPORT

A patient with Loeys-Dietz syndrome treated with chemoradiotherapy for an oropharyngeal carcinoma

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SUMMARY

We present the first published case of a patient with Loeys-Dietz syndrome (LDS) who was treated with radical chemoradiotherapy for an oropharyngeal carcinoma. In view of this newly recognised connective tissue disease, the uncertainty of severe toxicity from chemoradiotherapy to treat a potentially curative cancer posed a management challenge. The patient was treated with chemoradiotherapy and remains well with no evidence of recurrence at 3 years. Furthermore, we have observed minimal late effects secondary to chemoradiotherapy at 3 years following the completion of treatment suggesting that the underlying pathogenesis of LDS may provide an interesting human model to further elucidate the complex interactions of transforming growth factor β 1 (TGF- β 1) and tissue fibrosis secondary to chemoradiotherapy. A review of LDS as well as the association of TGF- β 1 expression and tissue fibrosis is presented.

BACKGROUND

Loeys-Dietz syndrome (LDS) is a newly recognised genetic connective tissue disease characterised by aggressive aortic and distal arterial aneurysms. It has been recently recognised as a separate disease to other genetic syndromes such as Marfan's syndrome (MFS) and Ehlers-Danlos syndrome. There is a paucity of literature describing the experiences of chemotherapy and radiotherapy in patients with cancer with connective tissue disorders particularly with regard to late toxicity. We present a challenging scenario of treating a potentially curative oropharyngeal carcinoma with chemoradiotherapy in a patient with LDS.

CASE PRESENTATION

A 45-year-old man presented with a left neck lump with no swallowing, speech or ear symptoms. Clinical examination showed hypertelorism and an oral inspection showed a high-arched palate. Oral and nasopharyngoscopic examinations showed no suspicious mucosal lesions in the upper aerodigestive tract. A total skin assessment was unremarkable. An ultrasound neck confirmed an enlarged left neck node and he underwent an excision biopsy confirming a poorly differentiated keratinising squamous cell carcinoma. Immunohistochemical staining was positive for p16 in keeping with human papillomavirus-associated disease. He had previously smoked 15 years ago (10 pack-years) and consumed no alcohol. He had a history of several family members needing aortic surgery. A positron emission tomography CT scan disclosed a marked fluorodeoxyglucose (FDG)-uptake within the left tonsil

(measuring 23 mm in maximum dimension, SUV 13.1), with no extension into the soft palate, base of tongue or parapharyngeal fat (figure 1). Several small FDG-avid nodes, with a maximum size of 11 mm, were seen in the left level II neck (SUV 4.6). No distant metastases were evident.

Figure 1 (A) Coronal view of positron emission tomography CT scan of head and neck showing marked fluorodeoxyglucose (FDG)-uptake within the left tonsil (SUV 13.1). (B) Axial view of positron emission tomography CT scan of neck showing two small FDG-avid left neck nodes (SUV 4.6).

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Figure 2 Histology of the aorta showed moderate mucoid degeneration of the media with elastic van Gieson special stain showing discontinuity and breakage of the elastic fibres.

He was diagnosed with LDS 3 years previously following an acute aortic dissection which required an aortic root replacement with a mechanical aortic valve. Histology of the aorta showed moderate mucoid degeneration of the media with an elastic van Gieson special stain showing discontinuity and breakage of the elastic fibres (figure 2). A molecular diagnosis of LDS was confirmed with a mutation identified in the transforming growth factor- β receptor 1 (TGF- β R1). A follow-up MRI from skull base to upper pelvis showed no other major vessels to be at significant risk of dissection. His medications included warfarin, bisoprolol, ramipril and losartan.

The patient was treated with chemoradiotherapy for a well lateralised T2N2bM0 left tonsillar squamous cell carcinoma. A tonsillectomy was not pursued in view of his anticoagulation and prolonged bleeding following his node excision biopsy. He was treated with conformal external beam radiotherapy; 66 Gy in 33 fractions over 6.5 weeks using 6 MV photons to the primary site and to the involved left neck nodes, with a matched anterior lower left neck field of 50 Gy in 25 fractions to the uninvolved left neck. Bolus was applied over the left neck nodes. He received concurrent carboplatin area under the curve (AUC) 4.5 during the first and fourth week of radiotherapy which he tolerated well with standard antiemetics as per our local policy. The patient developed G1 mucositis (Common Terminology Criteria for Adverse Events V4.03) in the second week of radiotherapy after 12 Gy. In the fourth week after 34 Gy, he developed G3 dysphagia associated with a 4% reduction in his weight compared with the baseline, and he started Fortisip supplements via a percutaneous endoscopic gastrostomy (PEG) feeding tube. In the final week of radiotherapy, he had G3 mucositis and G2 radiation-dermatitis, and he was managed on a fentanyl 25 μ g patch changed every 72 h. His weight was 6% less than his baseline. His full blood count and biochemistry remained satisfactory during treatment. The patient completed treatment in February 2010 with no unexpected acute toxicities, and his mucositis and skin reaction had healed at 6 weeks after the completion of treatment. His PEG feeding tube was removed 3 months following completion of treatment.

OUTCOME AND FOLLOW-UP

The patient was followed up every 6 weeks in the first year, every 8 weeks in the second year, and every 3 months in the third year. He remains alive and well with no evidence of recurrence and has only mild late toxicity at 3 years. He has G0

Figure 3 Telangiectasia in the oropharynx and high-arched palate.

dysphagia, G1 xerostomia, G0 trismus, G1 telangiectasia in the oropharynx (figure 3), G0 skin fibrosis, and G1 skin pigmentation over the left neck (figure 4) (LENT-SOMA criteria for late radiation toxicity). The last MR angiogram in 2012 confirmed no carotid vascular complications, in particular in the irradiated volume. This is the first published case of a patient with LDS treated with radical chemoradiotherapy for an oropharyngeal carcinoma. No unexpected acute toxicity and minimal late toxicity have been observed.

DISCUSSION

LDS is an autosomal-dominant connective tissue disorder first described in 2005 characterised by cardiovascular, craniofacial, neurocognitive and skeletal features.¹ It is associated with aggressive aortic and distal arterial aneurysms (intracranial, pelvic and abdominal sites) that are prone to early dissection, and this contrasts with MFS in which aneurysms are confined to the aortic root. The underlying aetiology of LDS are mutations in the genes encoding for the TGF- β receptor (TGF- β R), specifically chromosome 9q22 (TGF- β R1) and chromosome 3p22 (TGF- β R2).¹ Two distinct subtypes have been reported for which type I includes both craniofacial and vascular features (the triad of arterial tortuosity/aneurysms, hypertelorism and bifid uvula/cleft palate). Type II LDS has bifid uvula but has less severe vascular features and no craniofacial malformations.

The true prevalence of LDS is not yet known but is becoming increasingly recognised as a separate clinicopathological entity

Figure 4 Lack of skin fibrosis and mild skin pigmentation over the irradiated left neck.

to other genetic syndromes, such as MFS and Ehlers-Danlos syndrome, which share similar phenotypic features and therefore may have been previously misdiagnosed.^{2–3} LDS has a poorer outcome than other connective tissue diseases due to more severe aortic/arterial dissections, and therefore requires more frequent serial imaging and earlier surgical intervention. Aneurysms dissect at a smaller size and at an early age as compared to MFS.¹ The leading cause of death is dissection of the thoracic aorta (67%), followed by abdominal aorta dissection (22%) and intracranial bleeding (7%).⁴ The management of LDS is with β -blockers, life style measures such as exercise restriction to reduce haemodynamic stress and frequent imaging surveillance of the arterial tree with prophylactic surgical repair of the aortic root and other arterial aneurysms.⁴

The paucity of published literature of patients with connective tissue disorders receiving chemotherapy or radiotherapy posed a challenging scenario, in terms of choice of a concurrent systemic agent and radiotherapy target volumes, balancing the uncertainties of the toxicities with the potential for cure of an oropharyngeal carcinoma. There are currently no other reports of a patient with LDS treated with chemotherapy or radiotherapy for a malignancy. Our patient received carboplatin in view of the low risk of vascular or thrombotic complications, as experienced in a previous large series using carboplatin.⁵ The risks of these complications were estimated to be higher with cisplatin in view of the arterial tortuosity and aneurysms characteristic of LDS. The risks associated with cetuximab were deemed uncertain with no literature available regarding an interaction with epidermal growth factor receptor inhibition and abnormalities of TGF- β signalling. We also elected not to irradiate the right neck in order to minimise the long-term risks of contralateral carotid arterial complications in this case.

The patient tolerated treatment well with no unexpected acute or late effects. In fact, he has much milder late toxicity secondary to radiotherapy than expected when compared to the general population. He has mild skin pigmentation, no soft tissue fibrosis, no dysphagia and mild xerostomia which is due to the ipsilateral parotid receiving irradiation. It is well known that TGF- β 1 is overexpressed at sites of injury after radiotherapy and chemotherapy which underlies the development of tissue fibrosis.^{6–7} Furthermore, there have been several approaches of inhibiting TGF- β 1 function on normal tissue injury in the murine model. These have involved the use of antibodies or receptor tyrosine kinase inhibitors to prevent the binding of TGF- β 1 to its receptor and have been shown to be associated with less fibrosis, TGF- β 1 expression and signalling.^{8–9} The lack of soft tissue fibrosis seen in this case may be due to the fact that the underlying pathogenesis of LDS are mutations in TGF- β R, and therefore the downstream signalling of TGF- β 1 overexpression secondary to chemoradiotherapy are not manifested. Patients with LDS may provide an interesting human model to further elucidate the complex interactions of TGF- β 1

as well as the relationship between fibrosis and exposure to chemo-/radiotherapy. Given the limited published literature of patients with connective tissue diseases who have received chemo-/radiotherapy, we would encourage further reports in order to register a database of late effects and to aid future treatment decisions.

Learning points

- Loeys-Dietz syndrome is a newly recognised connective tissue disease separate to other genetic conditions such as Marfan's syndrome and Ehlers-Danlos syndrome.
- Loeys-Dietz syndrome is associated with a poorer outcome than Marfan's syndrome due to more severe aortic and arterial dissections, and requires frequent serial imaging and earlier surgical intervention.
- The presented case highlights the difficulty in managing a potentially curative cancer in a patient with a connective tissue syndrome which requires an open discussion regarding the risks and uncertainty of toxicities against the benefits of radical treatment.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Loeys BL, Chen J, Neptune ER, *et al.* A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005;37:275–81.
- 2 Yetman AT, Beroukhi RS, Ivy DD, *et al.* Importance of the clinical recognition of Loeys-Dietz syndrome in the neonatal period. *Pediatrics* 2007;119:e1199–202.
- 3 Drera B, Tadini G, Barlati S, *et al.* Identification of a novel TGFBR1 mutation in a Loeys-Dietz syndrome type II patient with vascular Ehlers-Danlos syndrome phenotype. *Clin Genet* 2008;73:290–93.
- 4 Loeys BL, Schwarze U, Holm T, *et al.* Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006;355:788–98.
- 5 Chan AK, Sanghera P, Choo BA, *et al.* Hypofractionated accelerated radiotherapy with concurrent carboplatin for locally advanced squamous cell carcinoma of the head and neck. *Clin Oncol (R Coll Radiol)* 2011;23:34–9.
- 6 Anscher MS, Peters WP, Reisenbichler H, *et al.* Transforming growth factor beta as a predictor of liver and lung fibrosis after autologous bone marrow transplantation for advanced breast cancer. *N Engl J Med* 1993;328:1592–8.
- 7 Novakova-Jiresova A, Van Gameren MM, Coppes RP, *et al.* Transforming growth factor-beta plasma dynamics and post-irradiation lung injury in lung cancer patients. *Radiother Oncol* 2004;71:183–9.
- 8 Anscher MS, Thrasher B, Rabbani Z, *et al.* Antitransforming growth factor-beta antibody 1D11 ameliorates normal tissue damage caused by high-dose radiation. *Int J Radiat Oncol Biol Phys* 2006;65:876–81.
- 9 Anscher MS, Thrasher B, Zgonjanin L, *et al.* Small molecular inhibitor of transforming growth factor-beta protects against development of radiation-induced lung injury. *Int J Radiat Oncol Biol Phys* 2008;71:829–37.

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