Anesthetic management of a patient with dyskeratosis congenita undergoing head and neck tumour dissection

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Abstract

Introduction: We present a patient undergoing head and neck tumour resection, in the context of dyskeratosis congenita, a genetic disorder resulting in progressive multi-organ failure. This is among the first case reports describing anaesthetic management of dyskeratosis congenita in the context of major surgery, and it highlights its challenging peri-operative care.

Case presentation: A 54-year-old Caucasian male presented for resection of a locally advanced oral tumour. He had liver disease and bone marrow failure as complications of dyskeratosis congenita. We managed his care with a multidisciplinary approach, and he recovered with an uncomplicated perioperative course.

Conclusion: This case report characterises the preparation required for managing dyskeratosis congenita in the context of major surgery. Given the paucity of anaesthetic literature about this rare disease, we have also broadly reviewed its multi-system manifestations and anaesthetic considerations.

Keywords: Dyskeratosis Congenita; Anaesthesia, General; Perioperative Care

Introduction

Dyskeratosis congenita, also known as Zinsser-Engman-Cole syndrome, is a rare disease of chromosome telomere biology. Although gradual shortening of telomeres sequences is a normal mechanism of cellular senescence, in dyskeratosis congenita the proteins responsible for preserving and maintaining telomeres are dysfunctional, leading to greatly accelerated telomere loss, with subsequent chromosomal instability and cellular dysfunction. This ultimately results in progressive multiorgan failure as cell lines in all tissues undergo premature aging. (1)

The inheritance pattern for dyskeratosis congenita is classically described as X-linked but in recent years uncommon autosomal dominant and autosomal recessive variants have been identified. DKC1 represents the most common gene mutation in the X-linked form of dyskeratosis congenita, accounting for up to 40% of cases, but other susceptibility genes have been identified, including: TERC, TINF2, ACD, RTEL1, TERT, CTC1, NHP2, NOP10, PARN, and WRAP53. (2-4) The incidence of dyskeratosis congenita is approximately 1 in 1 000 000, with a preponderance among males. Symptom onset is typically between 5 years and 12 years, (2) but severe forms may manifest in early childhood with additional neurologic (Hoyeraal-Hreidarsson syndrome) or ophthalmologic (Revesz syndrome) manifestations. (3)

Dyskeratosis congenita classically presents with the clinical triad of lacy reticular pigmentation of the upper chest and neck, nail dystrophy, and oral leukoplakia. (3) The disease results in other multisystem complications, summarised in Table 1. Of note, patients with dyskeratosis congenita have an elevated risk of head and neck tumours, among other malignancies. (1) Such tumours can present challenges to airway management, as they may be friable or risk airway obstruction; they may also be painful and impede voluntary mouth opening. The presence of poor dentition further compounds the difficulty in airway management, while concomitant pulmonary fibrosis also has obvious implications for ventilation and oxygenation. Patients often develop bone marrow failure, leading to thrombocytopenia and risk for haemorrhage. Liver dysfunction may also contribute to coagulopathy and result in altered clearance

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Table 1: Anesthetic considerations for dyskeratosis congenita.	
Anesthetic concerns	**Disease manifestation**
Difficult direct laryngoscopy	Poor dentition
	Dental crowding
	Tooth mobility
	Alveolar bone loss
	Friable tissue
	Oral leukoplakia
	Distorted anatomy
	Oral tumours
Restrictive lung disease	Pulmonary fibrosis
Hypoxemia	Pulmonary arteriovenous malformation
	Pulmonary fibrosis
	Pulmonary hypertension
	Ascites
Cardiovascular collapse	Right ventricular failure
Difficult insertion of transoesophageal probe, oro-/naso-gastric tubes	Esophageal stenosis
	Liver disease
	Portal hypertension
	Esophageal varices
Hemorrhage	Bone marrow failure
	Thrombocytopenia
	Anemia
	Liver synthetic dysfunction
	Transfusion-dependence
Infection	Leukopenia
Difficult insertion of foley catheter	Urethral stenosis
High risk for neuraxial anaesthesia, and deep peripheral nerve blocks	Coagulopathy

of anaesthetic medications.

Other manifestations of dyskeratosis congenita include pulmonary arteriovenous malformations, poor dentition, oesophageal stenosis, vascular ectasias, urethral stenosis, peripheral neuropathy, immunodeficiency, and accelerated aging. The specific constellation of dyskeratosis congenita manifestations is highly variable among patients, even among individuals of the same family. There is also an element of genetic anticipation in this disorder, where its manifestations can become more severe and present progressively earlier with successive generations. (3)

The treatment for dyskeratosis congenita is largely symptomatic. Androgen therapy with oxymethalone or danazol may improve cytopenias, as sex hormones have been suggested to promote telomerase function. (2) There are essentially no other effective options for medical management. Complications of bone marrow failure are the most common causes of death in this patient population, so haematopoietic stem cell transplant is considered when bone marrow failure is severe; however, long term outcomes from this intervention are still poor.

Case Report

A 54-year-old male was admitted prior to a head and neck tumour resection. He had a history of dyskeratosis congenita confirmed by genetic testing and was followed by specialists in another city for chronic bone marrow failure, in addition to Child Pugh B liver failure with cirrhosis, portal hypertension, oesophageal varices, and occasionally ascites. He was not transfusion dependent. Other comorbidities included hypertension, diet-controlled diabetes, and gastroesophageal reflux. His medications were furosemide, spironolactone, nadolol, hydroxyzine, and danazol. He had no medication allergies.

The patient had a squamous cell carcinoma

on the dorsal aspect of his tongue, which was painful and friable. Computed tomography imaging demonstrated a 4.2 cm mass without local extension or distant metastases. Nasopharyngoscopy performed by Otolaryngology showed a patent airway with easy vocal cord visualisation. There was no respiratory distress or airway obstruction. His airway examination was otherwise reassuring, with Mallampati score of 1, full mandibular protrusion and cervical spine range of motion. He had satisfactory mouth opening and thyromental distance, and normal dentition. Pre-operative blood work revealed thrombocytopenia with a platelet count of 16 x 109.L-1, and anaemia with a haemoglobin of 82 g.L-1; these values were consistent with his usual baseline. Transaminases, creatinine, electrolytes, PTT, and INR were all normal. Vital signs were unremarkable.

A post-operative Intensive Care Unit bed was reserved in case of intraoperative instability or bleeding. Haematology was consulted, for optimisation of his dyskeratosis congenita. His degree of bone marrow failure was almost sufficiently advanced to consider haematopoietic stem cell transplant, but this was deferred pending his cancer surgery. Since he was already on a stable androgen regimen with danazol, the primary recommendation to prevent excessive haemorrhage peri-operatively was to maintain his platelet count at greater than 50 x 109.L-1, via transfusion of single-donor platelets. Allowing for the possibility of significant intra-operative bleeding, a haemoglobin transfusion threshold of 70 g.L-1 was also suggested. His platelet count and haemoglobin responded appropriately to transfusion, but the gains were transient, so he required three units of platelets and two units of packed red blood cells during the three days preceding his operation. Immediately pre-operatively his haemoglobin and platelet count were 85 g.L-1 and 63 x 109.L-1, respectively. Additional units were made available in the operating room.

On the day of surgery, two large bore IVs and a radial arterial line were placed prior to induction. After pre-oxygenation, general anaesthesia was induced with sufentanil 10 mcg, propofol 250 mg, and rocuronium 50 mg, intravenously. Given the potential for airway obstruction or contamination from a friable oropharyngeal tumour, two functional

suction units were on hand and the surgeons had pre-emptively marked the patients' neck in the event of an emergency surgical airway. A video laryngoscope and a light wand were available as adjuncts. Fortunately, tracheal intubation was straightforward under direct laryngoscopy. Anaesthesia was maintained with sevoflurane 2% and a sufentanil infusion at 5 to 10 mcg.hr-1. The patient received tranexamic acid 1 g prior to incision. Cefazolin 2 g was given for surgical prophylaxis, and re-dosed after 4 hours. Using a rectal temperature probe and a forced-air warming device, normothermia was maintained. The tumour resection required a partial glossectomy, elective tracheostomy, and selective neck dissection with primary closure.

An intra-operative ROTEM showed no significant abnormalities. Total blood loss was approximately 500 mL, and the patient received 1.5 L of balanced crystalloid solution during the 6-hour operation. During the tumour resection, the patient's haemoglobin was trended via ABG, reaching a nadir of 80 g.L-1 upon conclusion of the operation. No intra-operative transfusion was required. Intensive Care Unit admission was deemed unnecessary, so he was transferred in stable condition to the post-anaesthetic care unit, then to the floor.

As per Haematology's recommendations, the goal was to maintain post-operative haemoglobin and platelet counts greater than 70 g.L-1 and 30 x 109.L-1, respectively. His platelet counts continually drifted below his transfusion threshold, so he accordingly received three bags of single-donor platelets over the course of four days. His haemostasis remained satisfactory and there was never clinical indication of haemorrhage. He remained in hospital for a total of nine days post-operatively, while his diet was advanced, and his platelet transfusion threshold was gradually relaxed by Haematology.

Discussion

Patients with dyskeratosis congenita present many potential challenges for anaesthetic care, given the diverse manifestations of their condition. Their accelerated telomere shortening and premature cellular aging results in progressive multiorgan failure starting in childhood, and the heterogeneous nature of the disorder makes every patient unique. A multidisciplinary approach can be helpful for pre-operative planning, and any choice to proceed with elective surgery should considered carefully in light of potential peri-operative risks. The patient in our case was mainly affected by progressive bone marrow failure, cirrhosis, and a tongue base tumour requiring resection.

Over 80% of persons with dyskeratosis congenita develop bone marrow failure, and consequently may have excessive or spontaneous bleeding, or susceptibility to infection.(5) However, the excessive use of blood products must be avoided, since their immunomodulatory effects may exacerbate pre-existing immunocompromise. Additionally, repeated exposure to transfused red cells or platelets may adversely affect the success of future stem cell transplantation, and chronically anaemic patients may also be adapted to tolerate lower baseline haemoglobin levels. (3) Nonetheless, when transfusion becomes necessary, blood products should be leukodepleted, irradiated, and CMV-negative.

In our case, a platelet transfusion threshold was recommended by Haematology to allow for acceptable haemostasis and mitigate the risk of excessive peri-operative haemorrhage. Bearing in mind the conflicting priority of minimising blood product transfusion, the use of blood conservation strategies is of course advisable for this patient population. As described in prior reports, we administered tranexamic acid to avoid fibrinolysis. (6) Our surgeons worked collaboratively with the anaesthesia team, and the importance of their careful surgical technique cannot be overstated. Topical haemostatic agents, including gelatin foams and epinephrine, were also available but were not required. We trended our patient's haemoglobin intra-operatively using serial ABGs and had immediate access to point-of-care thromboelastometry to guide our use of blood products in the event of major bleedin

It should be mentioned that our patient was on a stable androgen therapy regimen with danazol, one of the only agents helpful for slowing the progression of bone marrow failure in dyskeratosis congenita. Aside from stem cell transplantation as definitive treatment, there are almost no other options for medical optimisation of bone marrow failure in dyskeratosis congenita.

Our patient had liver disease, a complication affecting about 7% of persons with dyskeratosis congenita. (5) He fortunately did not have ascites at the time of surgery; however, consideration would have been made for paracentesis if there were significant ascites, since the increased intra-abdominal pressure could increase the risk of gastric reflux on induction while also reducing the safe apnoea time. Impaired liver synthetic function may also result in coagulopathy, independent of bone marrow failure. Chronic liver dysfunction may be associated with prolonged elimination of common anaesthesia medications, such as opioids, benzodiazepines, and neuromuscular blocking agents. It may therefore be reasonable to choose medications that are eliminated independently of liver function, for more predictable offset of medication effects.

Head and neck squamous cell carcinomas are very common in dyskeratosis congenita, and we made contingencies with our surgeons for the possibility of airway obstruction by our patient's tongue mass. Airway evaluation in these instances would not be complete without reviewing tumour anatomy on computed tomography imaging and/or inspection via nasopharyngoscopy. We also took care to avoid traumatising our patient's oral mucosa, since these surfaces are prone to bleeding in dyskeratosis congenita. Poor dentition and mandibular hypoplasia are potential disease manifestations that may further complicate airway management. Because of the well-characterised association between dyskeratosis congenita and oral tumours, most patients receive frequent monitoring of their oral health, yet it is still conceivable that an anaesthesia provider may be first to identify suspicious oral lesions in the course of a routine airway evaluation for unrelated procedures.(2)

Our patient did not have any respiratory impairment, but approximately 20% of persons with dyskeratosis congenita develop pulmonary complications, including interstitial lung disease, pulmonary arteriovenous malformations, pulmonary hypertension, shunting, or resultant right heart failure. These issues would present significant challenges for oxygenation and ventilation. The use of apnoeic oxygenation may be considered in the presence of severe pulmonary disease; however, prolonged hyperoxygenation therapy may exacerbate alveolar dysfunction, and would be discouraged. (3) Taking coagulation status and the surgical procedure into account, regional anaesthesia techniques may be favourable for patients with cardiopulmonary compromise. Clinical suspicion for pulmonary hypertension and right heart failure would warrant pre-operative EKG, echocardiography, and potentially intraoperative transoesophageal echocardiography. Unfortunately, transoesophageal echocardiography may be risky in the presence of oesophageal strictures or varices.

Finally, we paid close attention to aseptic technique and ensured appropriate antibiotic prophylaxis was given. Our patient had a normal white cell count and no history of recurrent or opportunistic infection, but persons with dyskeratosis congenita and bone marrow failure may be at risk for immune dysfunction. Incidentally, one of few anaesthetic case reports about dyskeratosis congenita described pre-operative administration of granulocyte colony-stimulating factor in an effort to improve white blood cell count (7); however, the co-administration of granulocyte colony-stimulating factor with androgens is controversial, owing to the related risk of life-threatening splenic rupture. (2)

At the present time, we are aware of only four other case reports specifically detailing anaesthetic care of this rare disorder, and most of them involved minor dental procedures. (7-10). The heterogeneous multisystem manifestations of dyskeratosis congenita make it a challenging condition in the peri-operative setting. Despite being described over a century ago, there is a striking paucity of literature describing its

anaesthetic care, and much further work is required to characterise its optimal peri-operative management.

Conclusion

This report highlighted the diverse anaesthetic challenges presented by patients with the rare genetic condition dyskeratosis congenita, when undergoing major surgery.

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