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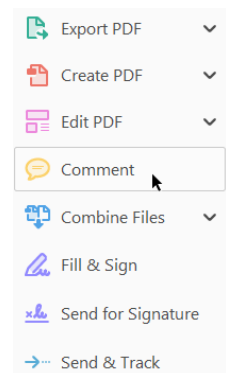
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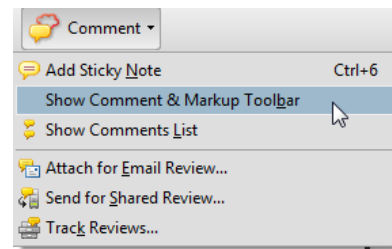


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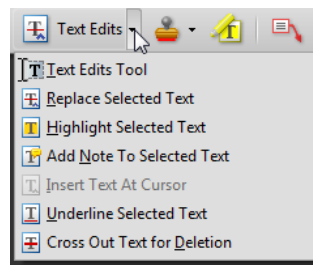


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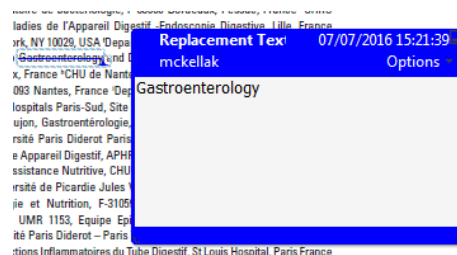
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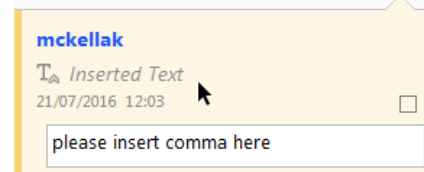


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CASE REPORT

A case report of successful treatment of high-output heart failure secondary to hereditary haemorrhagic telangiectasia with bevacizumab

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Abstract

Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder resulting in uncontrolled multisystem angiogenesis. The pathogenesis of this disease is thought to relate to elevated levels of transforming growth factor beta and vascular endothelial growth factor (VEGF). The frail arteriovenous malformations (AVMs) give rise to complications including haemorrhage and shunting. These have classically included recurrent epistaxis and gastrointestinal bleeding and associated iron-deficiency anaemia. More recently, high-output heart failure has been recognized in patients with significant hepatic involvement. This is thought to occur as a result of low systemic resistance due to shunting of blood through liver AVMs with an associated compensatory increase in cardiac output. Bevacizumab is a humanized monoclonal that acts to cause VEGF inhibition. Previously, this drug has been shown to benefit patients with HHT by reducing transfusion requirements and frequency of epistaxis. In addition, there is a growing body of evidence that bevacizumab may be associated with amelioration of high-output cardiac failure associated with HHT-induced hepatic shunting. We believe this case supports the use of bevacizumab in this context.

INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder with a reported incidence between 1:5000 and 1:8000 [1–3]. Three major HHT genes (ENG, ACVRL1 and SMAD4) have been identified, and more than 600 possible gene mutations associated with the development of clinical disease. The result of these mutations is a varied phenotype with the common characteristic of uncontrolled multisystem angiogenesis. Pathogenesis is thought to be related to elevated levels of transforming growth factor beta and vascular endothe-

lial growth factor (VEGF) that may be measured in affected patients. Complications arise from the disorganized, frail vessels that form that are susceptible to rupture as well as shunting due to arteriovenous malformations (AVMs). Classical features include spontaneous and recurrent epistaxis with mucocutaneous telangiectasia at multiple characteristic sites as well as gastrointestinal bleeding and associated iron deficiency.

More recently, high-output heart failure (HF) secondary to HHT with hepatic involvement has been reported. Low systemic resistance due to shunting of blood through liver AVMs is thought to lead to compensatory increased cardiac output

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and subsequent failure. Given the current understanding of the pathogenesis of the disease, it is plausible that VEGF inhibition with the humanized monoclonal antibody bevacizumab would alter the disease course and outcomes for patients with both cardiac and non-cardiac complications of HHT [4–6]. To date, there has been one reported positive phase 2 study examining the role of bevacizumab in 25 patients with high cardiac output as a result of HHT associated hepatic AVM [7].

CASE REPORT

A 77-year-old gentleman presented with HHT complicated by high-output HF as demonstrated on echocardiography. Multiple hepatic AVMs were seen on computed tomography (CT). Other medical history included peptic ulcer disease, obstructive sleep apnoea, cerebral vascular accident with minimal residual deficit, post-traumatic stress disorder secondary to military service overseas, pancreatic cysts and mild chronic obstructive pulmonary disease with distant smoking history. Family history was significant for 15 relatives also having a diagnosis of HHT. Prior to commencement of bevacizumab therapy, the patient had required frequent endoscopy and iron transfusions for many years. After exclusion of other causes of HF, the patient received bevacizumab treatment.

Echocardiogram was initially performed when the patient had been admitted to hospital with dyspnoea, orthopnoea, pedal oedema and considerable functional decline in the community. At that time, high-output HF was noted with resting cardiac index 5.6 Litres/minute/meter² (2.5–4 Litres/minute/meter²). Left ventricular size, function and wall thickness were considered to be normal, but mild right ventricular systolic dysfunction was noted. Brain natriuretic peptide was 1000 picograms/millilitre (<100 picograms/millilitre), and haemoglobin was 13.3 grams/decilitre (11.5–16.0 grams/decilitre). Small pleural effusions were noted on CT pulmonary angiogram, but no pulmonary AVMs were demonstrated. CT of the abdomen demonstrated altered vascularity in the liver and nodularity. This occurred in lobar distribution with nodularity and multiple rounded enhancing foci thought possibly to represent pseudo-cirrhosis. An enlarged portal venous system was noted.

A number of differentials for high-output HF were considered at the time of diagnosis. Anaemia is a known cause; however, iron studies were normal as was haemoglobin. It was thought that gastrointestinal blood loss had been diligently managed, and this was therefore unlikely the cause. Thyroid function was normal, and there was no sign of sepsis or myeloproliferative disorder. The patient was obese but not in the range previously reported to be associated with high-output HF. COPD-combined assessment class was A, and there were no previously documented exacerbations. Thus multiple AVMs of the liver were considered the most likely cause for high-output HF. A review of the literature was performed, and it was found that bevacizumab was considered a reasonable therapy given the molecular mechanisms of angiogenesis in HHT [4–8].

One of the limiting factors in the use of bevacizumab in Australia is the cost. For each treatment, the cost is ~\$AU3700, and this needs to be repeated every few weeks. The medication is not listed on the Pharmaceutical Benefits Scheme for this indication and is primarily prescribed for metastatic cancers. Our patient was unable to fund this treatment privately but was fortunate enough to be supported by the Australian Department of Veterans Affairs in his endeavour for treatment.

The patient underwent six treatment cycles of 12 weeks, receiving a dose every second week. On review after six cycles of

treatment, the patient had significant clinical improvement. There was no further orthopnoea or paroxysmal nocturnal dyspnoea. Pedal oedema had not recurred. There was no further haemoptysis or haematemesis and no melena over treatment months. The patients' haemoglobin had incremented to 16.0 grams/decilitre. There were no noted side effects from the bevacizumab. Repeat echocardiogram was performed and reported normalization of cardiac function. The patient continued to maintain an improved level of independence in the community with support from his son who lived with the patient. The patient will have ongoing echocardiograph surveillance and is considered likely to require further treatments in the future.

DISCUSSION

This case demonstrates significant clinical improvements in a patient with high-output HF secondary to HHT treated with bevacizumab. We believe this case adds to a growing body of evidence that supports bevacizumab efficacy in this circumstance. To date, there are no randomized control trials to address the question of bevacizumab use for cardiac complications of HHT, but a number of case reports exist as well as one reported positive phase 2 study [7–11].

Due to the current cost of ongoing treatment with bevacizumab for these patients, there are significant financial considerations in planning further research in this area. However, balanced against significant morbidity and possible mortality improvements for patients and families suffering from complications of HHT, the authors believe trials are warranted. The cost of bevacizumab treatment also needs to be weighed against other potential savings in this patient group including transfusions, gastric interventions and transplant.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest to declare. No funding received for or associated with the writing or publication of this case report.

FUNDING

There were no sources of funding for the production of this article.

ETHICAL APPROVAL

No approval is required.

CONSENT

The case is fully deidentified; however, the patient has provided written consent to publish the article. The patient has received a copy of the article in its current form.

GUARANTOR

Mark Flower.

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