CASE REPORT

Acquired von Willebrand's disease associated with epithelial myoepithelial carcinoma of the parotid salivary gland

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Accepted 21 July 2014

SUMMARY

This is the first case report of a patient with acquired von Willebrand's disease (AvWD) secondary to epithelial myoepithelial carcinoma (EMC) of the parotid salivary gland. This patient presented to haematology following an abnormal bleeding episode with von Willebrand factor Ristocetin cofactor (VWF:RCO) <5% and VWF:Ag 13%. He was diagnosed with AvWD. At the same time he was found to have a left parotid lump which was excised following a multidisciplinary team meeting. This was histologically reported as an EMC. Following excision, unusually this patient's AvWD did not resolve. Extensive investigation looking for other causes of the AvWD did not reveal any other potential cause; therefore, due to the similar timing of onset of both pathologies it is felt that the AvWD in this case is secondary to the EMC. This case report highlights the presentation, investigation and management of AvWD and parotid lumps as well as discussing proposed pathophysiological mechanisms for AvWD.

BACKGROUND

This is the first case report of a patient with acquired von Willebrand's disease (AvWD) secondary to epithelial myoepithelial carcinoma (EMC) of the parotid salivary gland.

AvWD is a rare disorder with 449 cases reported in published literature up to 2011.¹ It has been associated with multiple diseases, including lymphoproliferative and myeloproliferative disorders, malignancies, immunological disorders, as well as cardiovascular disorders.^{2–5} The non-haematological malignancies that AvWD has been associated with are Wilms' tumour,^{6–7} peripheral neuroectodermal tumours,⁸ Ewing's sarcoma,⁹ adrenocortical carcinoma,¹⁰ lung cancer¹¹ and gastric carcinoma,¹² however it has never been associated with a salivary gland malignancy.

EMC is an uncommon epithelial neoplasm, comprising approximately 1% of all salivary gland tumours. It is predominantly a tumour of the major salivary glands but they may also arise in minor salivary glands^{13–15} and rarely in extraoral sites such as the paranasal sinuses,^{13–14} pharynx¹⁴ and bronchus.¹⁶

This case report will highlight the presentation, investigation and management of AvWD and parotid lumps as well as discussing proposed pathophysiological mechanisms for AvWD.

CASE PRESENTATION

A 71-year-old man presented to the Haematology Department in University Hospitals Bristol due to

an episode of significant blood loss from a buccal laceration which lasted over 24 h in September 2011. At the time of this event he visited his dentist who felt that the laceration in his oral cavity was too small to explain the extent of his bleeding. He did not need a blood transfusion and his bleeding stopped spontaneously. Otherwise he had been feeling well without any significant weight loss, no change in bowel habit and no rectal blood loss or nosebleeds.

He had a previous uneventful dental extraction in 2010 and three inguinal hernia repairs, initially in the 1970s and one in 1990, all of which were uneventful. He has high-blood pressure, diet-controlled diabetes mellitus and was diagnosed with polymyalgia rheumatica in 2010 for which he was on a weaning dose of steroids. He also has a congenital malformation of his right forearm.

At presentation, he was taking felodipine, ramipril, prednisolone 6 mg weaning dose, omeprazole and alendronic acid. He had no children, lived alone and was a non-smoker and occasional drinker. He is an ex-engineer with no family history of abnormal bleeding or cancer.

On examination of his neck, a 3–4 cm firm, round swelling was palpable in the left parotid region. He mentioned that he had noticed it for roughly 1 year, however, since the significant bleeding episode, 4 months previously, it had grown rapidly. He had noticed no change in his salivary flow rate. His facial nerve function was normal. Apart from this there were no other symptoms or signs on history and examination.

Owing to his bleeding episode the ear, nose and throat (ENT) department felt it would be best to organise MRI of his head and neck and liaise with the haematology department regarding safely performing fine-needle aspiration (FNA) of the lump for cytology.

INVESTIGATIONS

The von Willebrand factor Ristocetin cofactor (VWF:RCO) was <5%, VWF:Ag 13% and factor VIII 6.1%. Therefore, due to these results and the late onset of an abnormal bleeding episode without a family history of vWD a diagnosis of AvWD was made.

An echocardiogram was performed to assess for cardiac causes of AvWD which showed good left and right ventricular function with no valvular pathology.

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To cite: Chilvers GS, Porter G. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-205248

The MRI with gadolinium enhancement showed a 3 cm multi-lobulated tumour in the left parotid gland in the anterior aspect superficially with clear boundaries and no evidence of invasion of the surrounding tissue. The mass had a focal area of signal dropout consistent with a degree of calcification. There was also a fluid level suggesting a previous haemorrhage (figure 1).

The parotid mass was aspirated and 20 mL of green/brown turbid fluid was removed. Cytology of the fluid demonstrated heavily blood-stained fluid containing foamy, haemosiderin laden macrophages and inflammatory cells, in keeping with cyst fluid. However, no epithelial cells were present to indicate the nature of the cyst. Overall this was insufficient for cytological diagnosis.

At the head and neck multidisciplinary team meeting it was concluded that this tumour was most likely a benign cystadenolymphoma (Warthin's tumour) and a capsular excision was recommended.

This operation was postponed for a few months as the patient was suffering from increasing chest pain at rest. A diagnostic angiogram was performed which showed triple vessel disease. The patient underwent coronary artery bypass surgery with detailed input from the haematology department. The operation was uneventful.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for abnormal mucosal bleeding include haemophilia A, haemophilia B, Bernard-Soulier syndrome, platelet function defects, antiplatelet and anticoagulant drug ingestion and fibrinolytic defects.

The differential diagnosis of a parotid lump can be divided into benign and malignant. Warthin's tumour was considered the most likely diagnosis. Other benign differentials include pleomorphic adenoma, oncocytoma and monomorphic tumours. Malignant differentials include mucoepidermoid carcinoma, adenoid cystic carcinoma, carcinoma ex-pleomorphic adenoma, squamous cell carcinoma, anaplastic or undifferentiated carcinoma acinic cell carcinoma, polymorphous low-grade adenocarcinoma and lymphoma. In addition to benign and malignant tumours, the differential diagnosis also includes salivary cysts, cysts of the first branchial cleft, salivary gland stones, sarcoid, Sjögren's syndrome, metastases from other tumours, lymphoepithelial cysts (particularly in an immunocompromised patient), chronic sclerosing sialadenitis (Küttner's tumor) and

regional lymphadenopathy from infectious, inflammatory or malignant diseases.

TREATMENT

The AvWD responded very well to intravenous immunoglobulins (IVIG). The haematology department continued to monitor him and prescribed IVIG when required.

A left partial parotidectomy was performed with detailed advice from the haematology department. Preoperatively he received IVIG 3 and 2 days before the operation. Immediately prior to the procedure two units of cryoprecipitate were given. During the operation a tense cystic left parotid mass superiorly in the gland overlying multiple upper facial nerve branches was evident. Capsular dissection of the mass was undertaken due to the proximity of facial nerve branches. Haemostasis was achieved and a 3.3 mm diameter vacuum drain was inserted. 1 h postoperatively the drain had collected 185 mL of blood and a facial haematoma was present. The vacuum on the drain was increased and the haematoma was aspirated. The consultant haematologist recommended two further units of cryoprecipitate and 1 g of tranexamic acid. The facial haematoma settled and the drain was removed on day 2 postoperatively. Following this the facial haematoma recollected multiple times requiring four aspirations. This led to a wound infection which resolved with intravenous cefuroxime and metronidazole. A wound swab and blood cultures did not grow any pathogens.

Histological assessment of the tumour demonstrated a part solid, part cystic tumour 45 mm in maximum dimension. The microscopic features were consistent with EMC. There was no evidence of lymphovascular or perineural invasion. Excision appeared to be complete but the margin was 1 mm in places. There were two intraparotid lymph nodes identified, neither had evidence of metastasis. Pathological tumour staging was pT3.

The head and neck multidisciplinary team recommended observation with a MRI of the head and neck with gadolinium 6 months postoperatively. This showed no evidence of recurrent disease (figure 2).

OUTCOME AND FOLLOW-UP

There continues to be no sign of recurrence 16 months after surgery, however his AvWD persisted despite resection of the

Figure 1 MRI with gadolinium enhancement of the head and neck showing the left parotid tumour.

Figure 2 MRI with gadolinium enhancement of the head and neck showing no recurrence of the left parotid tumour.

parotid tumour. Therefore, a CT scan of his chest, abdomen and pelvis was requested in May 2013 which did not identify any abnormality.

He continues to visit the Bristol Haemophilia Centre on a monthly basis for IVIG in order to maintain his VWF levels.

DISCUSSION

Approximately 80% to 85% of salivary gland tumours occur in the parotid gland,^{17 18} of which approximately 20% are malignant. They usually present as a painless, asymptomatic mass, however, sometimes they may be painful suggesting perineural invasion. If facial weakness is present it is generally indicative of a malignant tumour.

The most important investigation before considering surgery for treatment and diagnosis is FNA cytology which has been shown to have sensitivity and specificity for correctly interpreting a mass as benign or malignant of 73% and 91%, respectively.¹⁹ Ultrasound can often provide high-quality resolution and tissue characterisation helpful for diagnosis and is often used in assisting FNA.

Both CT and MRI can be used to assess the extent of a salivary gland tumour evaluating local, bony and perineural invasion, and lymph node metastases. MRI permits more detailed evaluation of soft tissue infiltration, perineural invasion and intracranial extension.²⁰ In addition, CT or MRI can provide anatomic details that are useful for surgical planning.

EMC is an uncommon epithelial neoplasm, comprising approximately 1% of all salivary gland tumours. It is predominantly a tumour of the major salivary glands but they may also arise in minor salivary glands^{13–15} and rarely in extraoral sites such as the paranasal sinuses,^{13 14} pharynx¹⁴ and bronchus.¹⁶

The peak incidence is in the seventh decade of life with the mean age being 60 years. Approximately 60% of the patients are female.

Although originally thought to be benign in a review of 35 cases²¹ 37% had recurrences and 17% lymph node metastases. Three patients developed distant metastatic spread and died 9 months, 10 years and 27 years after initial diagnosis. EMC is now considered a low-grade malignancy according to the WHO Salivary Gland Classification.

For many authors, a complete surgical resection is the only and best treatment for EMC. Deere *et al*²² reported that adjuvant radiotherapy might be effective in preventing local recurrence.

Information on the effectiveness of different treatments is scanty. In one series of nine patients²³ seven were initially treated by surgical excision alone and five later developed one or more recurrences. In contrast, both patients treated with surgical excision plus immediate postoperative radiotherapy remained tumour free after 9 years. In another study²⁴ four patients were treated with surgical excision, one of which received a course of radiation shortly after surgery. One of the patients who was treated with surgical excision alone later had a recurrence.

In the present case, as the tumour is a low-grade malignancy and excision was considered to be complete it was decided that no radiotherapy was required.

AvWD was first described in 1968 in a patient with systemic lupus erythematosus.²⁵ It presents with similar features to congenital vWD with regard to clinical and laboratory parameters. The key distinguishers of AvWD is its late onset of bleeding diathesis without a family history of vWD and no history of prolonged bleeding after previous haemostatic challenges.²⁶ vWD occurs when VWF is sufficiently decreased in the plasma

or when a qualitative defect in VWF impairs one of its functions. VWF is a large multifunctional glycoprotein that performs two critical functions in haemostasis: it acts as a bridging molecule for platelet adhesion and aggregation at sites of injury and acts as a carrier for factor VIII in the circulation rendering stability to the molecule.²⁷

In vWD these abnormalities mostly affect platelet plug formation during the primary haemostatic response. As a result, many of the usual clinical manifestations of vWD are similar to those seen in platelet disorders. These include: easy bruising, skin bleeding and prolonged bleeding from mucosal surfaces.

AvWD is a rare disorder which has been associated with multiple diseases, most frequently including lymphoproliferative and myeloproliferative disorders, malignancies, immunological disorders, as well as cardiovascular disorders.^{2–5} The cardiovascular disorders most commonly associated with AvWD include: aortic stenosis,²⁸ mitral valve prolapse, congenital ventricular or atrial septal defects^{29 30} and after implantation of ventricular assist devices.^{31 32}

While AvWD has been associated with the following non-haematological malignancies: Wilms' tumor,^{6 7} peripheral neuroectodermal tumours,⁸ Ewing's sarcoma,⁹ adrenocortical carcinoma,¹⁰ lung cancer¹¹ and gastric carcinoma.¹²

There are multiple proposed pathophysiological mechanisms for AvWD. The most accepted theory for AvWD to be secondary to a tumour is the absorption of VWF multimers by the tumour cells.¹ Other proposed theories include: autoantibodies against VWF and proteolysis of VWF molecules by shearing forces.

Interestingly, in this case the AvWD did not resolve once the tumour was excised as expected from previous cases of AvWD secondary to a malignancy. However, further investigations looking for another cause of AvWD did not produce any alternative results. Ischaemic heart disease is not considered a cause of AvWD while the coronary artery bypass surgery was performed after the AvWD had been diagnosed. Therefore, due to the similar timing of onset of both pathologies it is felt that the AvWD in this case is secondary to the EMC of the parotid salivary gland.

Learning points

- ▶ Acquired von Willebrand's disease can be secondary to salivary gland malignancies such as epithelial myoepithelial carcinoma.
- ▶ All management decisions regarding head and neck tumours should be made in a multidisciplinary team meeting, importantly taking the patient's preferences into account.
- ▶ When performing a surgical procedure on a patient with a bleeding disorder it is important to have haematological advice and support.

Contributors GSC researched and wrote up the case report. GP is the ENT Consultant looking after this patient who edited the case report.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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