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Main Articles

Consumptive coagulopathy complicating juvenile angiofibroma

CAMPBELL BAGULEY, M.B.CH.B., GURI SANDHU, F.R.C.S., JAMES O'DONNELL, PH.D., M.R.C.PATH.*, DAVID HOWARD, F.R.C.S., F.R.C.S.(ED.)

Abstract

Objective: To investigate the incidence and clinical significance of deranged clotting results among patients with juvenile (nasopharyngeal) angiofibroma.

Methods: Twenty consecutive patients treated for juvenile angiofibroma between March 1998 and July 2002 in whom preoperative coagulation tests were performed were selected. Results were compared with normal laboratory values, and clinical and histological records were retrospectively analysed.

Results: Four out of 20 patients were found to have abnormal tests, consistent with concurrent consumptive coagulopathies. One patient was found to have a raised D-dimer level. This resolved following removal of the lesion.

Conclusions: The association between larger arterio-venous malformations and disseminated intravascular coagulopathy is well described (Kasabach–Merritt syndrome). Our findings suggest that low-grade consumptive coagulopathies may also complicate smaller juvenile angiofibromas, implying that preoperative coagulation screening tests may have a role in ensuring optimal perioperative haemostasis.

Key words: Angiofibroma; Coagulopathy; Disseminated Intravascular Coagulation; Kasabach–Merritt Syndrome

Introduction

Giant haemangiomas are frequently associated with coagulopathies, in particular chronic disseminated intravascular coagulation (DIC). In 1940, Kasabach and Merritt[1] first described a syndrome of "capillary haemangioma with extensive purpura", and many subsequent reports have confirmed this observation. In this setting, DIC results in a consumptive coagulopathy, with thrombocytopenia and deficiency of fibrinogen, factor V and factor VIII. The mechanisms by which vascular lesions precipitate intravascular coagulation are complex and include stasis, endothelial cell dysfunction and endothelial cell damage. Moreover, mechanical damage to red blood cells passing through the vascular malformation can result in development of a microangiopathic haemolytic anaemia.

The development of DIC and consumptive coagulopathy in a patient with a vascular malformation is of major clinical significance, particularly in terms of achieving adequate perioperative haemostasis. Disseminated intravascular coagulopathy can be either acute or chronic. In acute, uncompensated DIC, the patient develops marked coagulopathy and thrombocytopenia. Such patients are often profoundly unwell, and bleeding manifestations are common (within the skin, gastrointestinal tract, orbit, lungs, central nervous system, etc.). Moreover, development of significant intravascular thrombi can also result in multiorgan dysfunction (e.g. in the kidneys, liver, lungs and central nervous system).

Chronic or low-grade DIC is an entirely distinct clinical entity to acute DIC, although the underlying pathophysiology is identical. In chronic DIC, the patient is able to compensate and is typically asymptomatic. Consequently, routine laboratory coagulation testing in such patients demonstrates only subtle abnormalities. The platelet count may be reduced, fibrinogen levels normal or high, and the prothrombin time (PT) and activated partial thromboplastin time (APTT) may be within normal limits or slightly prolonged. Previous studies have

From the Royal National Throat, Nose and Ear Hospital, London, UK, and the *Department of Haematology, Royal Free Hospital School of Medicine, London, UK.
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TABLE I

PREOPERATIVE BLOOD TEST RESULTS AND TUMOUR VOLUMES

Patient	PT (sec) [12–16]	APTT (sec) [28–38]	D-dimers (μg/l) [1–130]	Platelets ($\times 10^9$/l) [140–400]	Tumour volume (cm^3)
1	15.4	34.7	-	460 ↑	-
2	13.6	25.5	-	289	-
3	14.9	32.8	-	316	-
4	16.5 ↑	33.9	-	228	-
5	14.2	32.3	-	320	2
6	14.3	34.7	-	191	-
7	14.7	31.7	-	472 ↑	-
8	15.0	32.7	-	252	60
9	14.8	25.7	-	297	210
10	14.1	32.5	-	356	45
11	19.0 ↑	34.0	-	212	60
12	15.1	31.2	-	329	-
13	12.3	32.3	-	296	-
14	15.9	35.0	-	294	120
15	15.0	36.9	-	337	200
16	15.6	42.7 ↑	1000 ↑	279	24
17	15.2	36.5	-	313	52
18	13.3	27.3 ↓	130 ↑	242	20
19	16.3 ↑	36.4	88	329	30
20	14.9	32.0	103	267	14

Normal values are given in square brackets. Arrows indicate values outside the normal range.

clearly shown that raised levels of fibrinogen degradation products (FDPs) and D-dimers can be used to identify patients with compensated chronic DIC (i.e. a normal coagulation screen in the presence of some ongoing consumptive coagulopathy).[2]

Juvenile angiofibroma is an uncommon vascular lesion of the nasopharynx which affects adolescent males. It has a high bleeding tendency and high reported rates of recurrence. It is diagnosed by its clinical presentation along with computed tomography (CT) or magnetic resonance imaging.[3] Numerous methods of removal have been employed. Mid-facial degloving is often favoured due to the good access provided to the skull base and low rates of recurrence.[4] We hypothesized that juvenile angiofibroma may also be associated with development of chronic DIC, which may explain subtle laboratory abnormalities observed and contribute to the bleeding tendency associated with its removal. To investigate this hypothesis, we studied routine preoperative coagulation screening tests in a cohort of patients with confirmed nasopharyngeal angiofibroma. For patients whose results were most suggestive of a consumptive coagulopathy, postoperative monitoring was carried out. All the patients were operated on at the Royal National Throat, Nose and Ear Hospital, London.

Methods

Between 1998 and July 2002, 20 patients were referred to the Royal National Throat, Nose and Ear Hospital, London, for management of nasopharyngeal angiofibroma and had preoperative coagulation screening performed. In all cases, histological confirmation of the diagnosis was made postoperatively.

These 20 individuals were selected for further investigation by examination of clinical records. Routine coagulation screening consisted of full blood count, prothrombin time and activated partial thromboplastin time. D-dimer levels were performed on four patients and thrombin and reptilase times on one patient whose D-dimer level was raised. All tests were performed in the Katherine Dormandy Haemophilia Centre and Haemostasis Unit at the Royal Free Hospital, London, according to standard published techniques. The normal ranges were established for each assay using a group of normal individuals, and the values quoted represent two standard deviations either side of the mean.

Histology reports were examined to investigate tumour size. For the other eight patients there was inadequate information on histology reports. Reports made calculation of tumour volume possible for a total of 12 patients.

Results

Twenty individuals in whom preoperative coagulation screening was performed were selected for further investigation. The age range in this group was 11–32 years (mean 17 years). While intermittent epistaxis from the nasal lesion is a frequent symptom of juvenile angiofibroma, there was no other history of bleeding tendency in this group. Preoperative full blood counts were performed on all patients. Reduced haemoglobin levels were seen in three patients, each of whom had a history of recent epistaxis.

The results of preoperative coagulation screens and platelet levels for the 20 patients are presented in Table I. Four patients (numbers 4, 11, 16 and 19) were identified in whom the coagulation screen was abnormal. Patients 4, 11 and 19 demonstrated isolated prolongation of the prothrombin time (16.5, 19.0 and 16.3 sec, respectively). All underwent uneventful resection of the lesions. There was no excessive peri-operative blood loss, and no blood transfusion was required.

Patient 16 displayed the most abnormal results. The APTT was prolonged at 42.7 sec (normal value 28–38 sec). Moreover, the D-dimer level was markedly elevated at 1000 μg/l (normal value 1–130 μg/l). Thrombin time and reptilase times were within normal limits. The tumour's size was 40 × 30 × 20 mm (volume 24 cm^3, average for the series 70 cm^3). The preoperative CT scan, showing typical features, is shown in Figure 1 and the histology in Figure 2. In spite of having laboratory findings consistent with low-grade chronic DIC, the patient had no significant bleeding history and surgery was uncomplicated. Although packed cells were cross-matched pre-operatively, no transfusion was required. Haemoglobin was 17.2 g/dl preoperatively and 13.1 g/dl postoperatively. Following the successful surgical resection, serial coagulation screening tests were performed. The D-dimer level had reduced to 242 μg/l 11 days later and was normal 35 days post-surgery. The thrombin and reptilase times remained within normal limits, as did the platelet count. The APTT remained elevated at 43.0 sec.

Tumour volume was estimated from histopathology reports where possible (12 patients). The volume range was 2–210 cm^3 (mean 69.75 cm^3). The mean tumour volume in three patients who displayed evidence of a coagulopathy (patients 11, 16 and 19) was 38 cm^3.

Interestingly, histology in one small tumour (patient 5, 2 × 1 × 1 cm) demonstrated vascular thrombi and areas of infarction, while the coagulation screen in this patient was normal. The reporting pathologist in fact considered intraluminal thrombi to be usual for these lesions. An example is shown in Figure 2.

Discussion

Traditional teaching describes normal haemostasis as occurring by two independent pathways, the intrinsic and extrinsic pathways. However, recent studies have clearly shown that this concept does not accurately reflect *in vivo* haemostasis.[5] Instead, coagulation *in vivo* involves a single pathway that is initiated when vascular-wall damage results in exposure of blood to tissue factor (TF). This TF is expressed on the surface of many extravascular cells but is normally absent from cells in direct contact with blood. When exposed (through trauma, burns, sepsis, cancer, autoimmune disorders and vasculitis, or through other sources of tissue damage), TF binds to circulating factor VII. This factor VII bound to tissue factor undergoes limited proteolytic cleavage to produce the active serine protease factor VIIa. The resultant high-affinity TF–VIIa complex can then activate factors IX and X, thus triggering thrombin generation at the site of vascular damage. This thrombin can cleave fibrinogen to produce a stable fibrin clot.

In normal situations, the coagulation pathway is kept in balance. Dysregulation of the coagulation cascade results in DIC and represents a well recognized complication of vascular malformations. Pathological widespread intravascular thrombin generation induces deposition of fibrin, vessel obstruction and the consumption of haemostatic factors such as platelets, fibrinogen, protein C and antithrombin-III. Moreover, secretion of plasminogen activator from endothelial cells mediates compensatory thrombolysis. The by-products of thrombolysis can then further increase the risk of significant clinical bleeding by interference with normal clotting mechanisms.

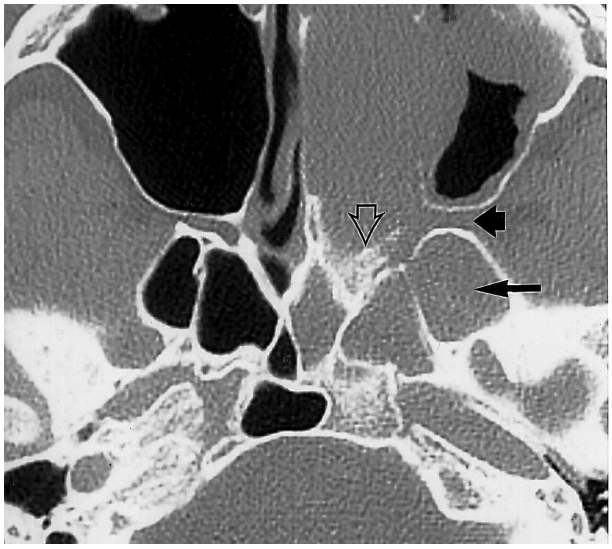

FIG. 1

Axial CT image showing some typical features of angiofibroma (patient 16): widening of the pterygopalatine fossa (short arrow), bone erosion at the anterior end of the pterygoid canal (hollow arrow) and retained secretions in the spenoid sinuses (long arrow). Mucosal thickening is present in the left maxillary antrum.

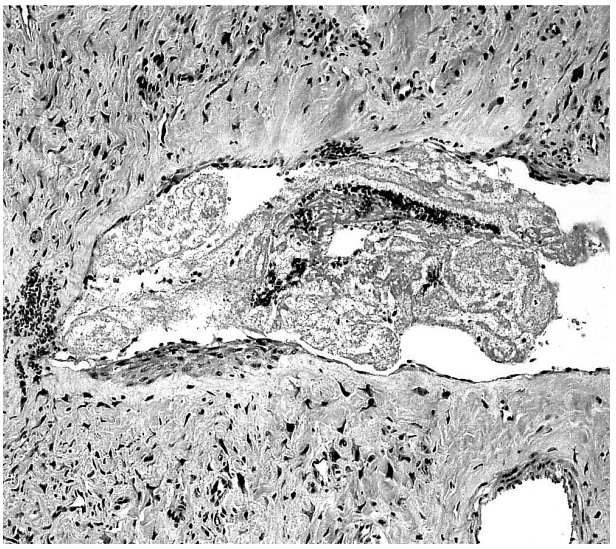

FIG. 2

Histological slide of angiofibroma (patient 16). A typical fibrous stroma is shown, along with dilated blood vessels. A large fibrin thrombus fills the central vessel (H&E stain, original magnification ×150).

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Although acute, uncompensated DIC is a life-threatening complication, as seen in the Kasabach–Merritt syndrome, it is more common for vascular malformations to be associated with a chronic, low-grade DIC.[6] Although these individuals will have some ongoing intravascular thrombin generation, with associated consumption of coagulation factors, the condition may not be evident clinically.

- **The potential for large vascular malformations to cause disseminated intravascular coagulation (DIC) is well described**
- **In a previous study (*Laryng Rhinol Otol* 1978;57:612–615) two patients with juvenile angiofibroma were found to have latent DIC that became manifest either during or following surgery**
- **In this study of 20 patients with angiofibroma the clotting mechanism was found to be suggestive of a low-grade, chronic DIC in three cases, with confirmatory elevated D-dimers in one other patient. There was no increased bleeding tendency in any patients described in this paper.**
- **The authors conclude that the clotting mechanism should be checked pre-operatively in all patients presenting with this condition and that post-operatively the same examination should be repeated to ensure that any higlighted abnormalities have resolved**

The optimal management of acute DIC remains unclear. However, adequate platelet concentrate and coagulation factor replacement [in the form of fresh frozen plasma (FFP) and cryoprecipitate] are essential to control any active bleeding.[6] The potential role for heparin in the management of acute DIC remains controversial. It is important to emphasize that in the majority of patients with low-grade, chronic DIC, no treatment will be indicated. However, if associated with active bleeding, platelets, FFP and cryoprecipitate may be required. Furthermore, several authors have reported the use of tranexamic acid to correct vascular malformation-associated coagulopathy.[7] This may be particularly useful in cases with evidence of underlying primary fibrinogenolysis.

The pathophysiology underlying development of consumptive coagulopathy in patients with vascular malformations is not fully understood. In a study of 13 paediatric patients, Alvarez-Mendoza *et al*.[8] proposed that an unknown trigger in lesions associated with Kasabach–Merritt syndrome caused accumulation of platelets, activation of the coagulation sequence and subsequent secondary fibrinolysis. Histology in all cases demonstrated benign vascular 'neoplasms' as the underlying lesion. In approximately 80 per cent of these cases, the dominant morphologic components consisted of tufted angioma or kaposiform haemangioendothelioma. It is believed these are both variations of haemangioma. The other patients in this group were shown to have infantile haemangiomas. The histological nature of juvenile angiofibroma has also been found to represent vascular malformation rather than true neoplasm.[9] Series of larger lesions have demonstrated local intravascular coagulation in as many as 88 per cent of patients.[10] Such lesions typically result in consumption of platelets and fibrinogen due to local intravascular thrombus generation and excessive fibrinogenolysis. There is presumably local activation of the coagulation pathway (described above) and release of tissue plasminogen activator by the abnormal endothelial lining of the 'tumour' cells.

Our findings are consistent with these previous reports identifying consumptive coagulopathy as a complication of vascular malformations in general. We found laboratory evidence of low-grade, chronic DIC in four of 20 patients with objectively confirmed juvenile angiofibroma. Clearly, the histologic irregularities characteristic of juvenile angiofibromas can thus also result in platelet aggregation and coagulation pathway activation. In keeping with previous reports on patients with Kasabach–Merritt syndrome, we found no relationship between tumour size and degree of underlying coagulopathy.[6] Difficulties with haemostasis have been encountered in cases of juvenile angiofibroma and attributed to underlying clotting derangement.[11,12] However, it is important to emphasize that we found no association between laboratory-confirmed coagulopathy and any perioperative haemorrhagic or thrombotic complications. One of the patients studied demonstrated a marked coagulopathy which resolved rapidly following surgery. Although his surgery was not complicated by excessive bleeding, this case demonstrates the potential for clinically significant chronic DIC to develop in association with juvenile angiofibroma. Consequently, we advocate preoperative coagulation screening tests (comprising PT, APTT, fibrinogen and FDPs) in all such cases.

Conclusion

In conclusion, our results have the following implications for the patient with juvenile angiofibroma.

(1) A history of abnormal bleeding should be sought in all patients with this disease.
(2) Preoperative coagulation screens should be performed on all patients after their diagnosis is confirmed radiologically.
(3) Specialist haematological advice is required should abnormalities be detected.
(4) Close perioperative monitoring is required for all patients, particularly if blood loss is excessive and transfusion required.
(5) Follow-up in such patients should include tests of prothrombin time, activated partial thromboplastin time and D-dimers to confirm that abnormalities resolve.

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Address for correspondence:
Mr G. Sandhu,
Great Ormond St Hospital for Children,
Great Ormond St,
London
WC1N 3JH, UK.

E-mail: campbell@baguley.ws

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