

Autoimmune Haemolytic Anaemia and Anastomosing Haemangioma: A Possible Relationship

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1. Abstract

This study presents the case of a patient with autoimmune haemolytic anaemia and an anastomosing haemangioma. The main dilemma is whether or not there is a relationship between the two processes and how both issues should be managed. The diagnostic methods used were analytical and imaging techniques, which proved to be inconclusive for the diagnosis of anastomotic haemangioma. Preoperative treatment with corticosteroids did not prevent anaemia, platelets, and elevated levels of total reticulocytes in the postoperative period. Surgical indication was based on with reference to the progression of proliferative activity, with tumour enlargement and the compression of the vena cava over time. The procedure involved the total surgical resection of the tumour. The indication for surgical treatment of the anastomosing haemangioma and the decrease in alpha-fetoprotein after tumour resectioning are the most relevant data, although alpha-fetoprotein increased again after a few weeks. Angiogenesis resulting from the formation of erythroblastic islands in the tumour periphery, and clonal expansions may be a compensatory mechanism of haemolysis caused by autoimmune haemolytic anaemia. In conclusion, erythropoietic clonal proliferation in anastomosing haemangioma may be secondary to autoimmune haemolytic anaemia and compensates for the loss of red blood cells in bone marrow affected by senescence. Therefore, a possible causal relationship between

autoimmune haemolytic anaemia and anastomosing haemangioma is proposed.

2. Introduction

Autoimmune haemolytic anaemia is an acquired haemolysis caused by the dysfunction of the patient's immune system, which produces directed auto-antibodies against erythrocyte surface antigens [1]. The disease is defined by positive monospecific direct anti agglutination [2]. The WHO 2020 classification of soft tissue tumours recognises anastomosing haemangioma as a distinct benign vascular neoplasm [3]. The incidence of anastomosing haemangioma with a specific retroperitoneal location is rare and therefore not widely documented in the literature; if autoimmune haemolytic anaemia is added, there are no references. This tumour has been described in all age groups, from 2 to 85 years, with a median age of 65 years for non-renal tumours [4]. Anastomosing haemangiomas of the genitourinary tract are benign vascular neoplasms formed by thin-walled anastomosed, with scattered endothelial cells and infrequent mitoses. Multi-layered endothelial cells are absent. Vascular thrombi are typical, and lesions show areas of central sclerosis and focal necrosis [5]. In addition, prominent extra-medullary haematopoiesis and the immunohistochemical expression of CD31 and CD34 are observed [6]. The CD31 antigen (PECAM-1, plaque endothelial cell adhesion molecule-1) is a transmembrane glycoprotein that acts as an adhesion molecule

for vascular endothelial cells and platelets [7]. It plays an important role in angiogenesis. CD34 is a transmembrane glycoprotein belonging to the sialomucin family. It is selectively expressed on haematopoietic precursor stem cells, small vessel endothelial cells, embryonic fibroblasts, adipocytes, and tumour cells of endothelial origin [8]. Mutations in the GNA11, GNAQ and GNA14 genes are essential drivers in the pathogenesis of anastomotic haemangiomas [9]. Anastomosing haemangioma develops in more than 69% of cases due to recurrent activating mutations in the GNAQ gene, which encodes the alpha subunit of guanine nucleotide-binding protein G(q) (P50148). This protein interacts with cell membrane receptors to activate signal transduction pathways such as the MAPK pathway [10]. The presence of a recurrent mutation in anastomosing haemangioma implicates the GNAQ gene as a driver of its pathogenesis and confirms its clonal nature [11]. These mutations have been observed among others in haematological tumours [12]. Although there is no directly established association between abnormal G-protein-coupled receptor activity and autoimmune haemolytic anaemia, these receptors and their signalling pathways may be indirectly involved in its pathogenesis by way of immune mechanisms. All components of the immune system, including auto-antibodies, cytokines, and the complement system, among others, are involved in the pathogenesis of autoimmune haemolytic anaemia. The clinical presentation and treatment of autoimmune hemolytic anaemia are influenced by many factors, including the type of anaemia, degree of hemolysis, underlying diseases, presence of concomitant comorbidities, bone marrow compensatory abilities and the presence of fibrosis and dyserythropoiesis [13]. Multiple studies have shown that platelet-derived growth factor (PDGF) can act as a potent pro-migratory factor for cells of mesenchymal origin [14]. Vascular tumours that over-express platelet growth factor receptor- β (PGFR- β) can stimulate platelet production and angiogenesis, promoting the formation of new blood vessels [15]. Therefore, we hypothesise that there may be link between autoimmune haemolytic anaemia and anastomosing haemangiomas. However, the questions of how these two processes are connected and what will result from the surgical resectioning of the tumour remain unanswered at present. The aim of this clinical case is to illustrate the difficulties presented in the differential diagnosis of anastomosing haemangioma and the suitability of surgical interventions in the context of a patient with autoimmune haemolytic anaemia. Likewise, we analyse the pre- and postoperative treatment of the autoimmune haemolytic anaemia.

3. Case Reports

3.1. History and Physical Exam

An 80-year-old man, a professional cyclist in his youth, consulted on 22 March 2023 for a retroperitoneal inter-aorto caval tumor, diagnosed by CT scan in 2022. In his personal history, he consulted in 2020 with symptoms of asthenia and weight loss and had a diagnosis of autoimmune haemolytic anaemia. The patient did not respond to first-line treatment with 1 mgr./kg corticoid. The last dose of the second line of treatment with Rituximab (4 dose), was in 2021. He had Covid-19 in 2022, and then vaccinated. He also had hepatitis B Ag (-), Ac core (+) and had undergone cholecystectomy and prostatectomy. Physical examination reveals epigastric pain.

4. Laboratory Tests

4.1. Preoperative

In order to rule out extra-adrenal pheochromocytoma and carcinoid tumour, catecholamines, normetanephrine and metanephrine were determined in blood and urine. Urine tests for adrenaline, dopamine and noradrenaline were also normal, as were serotonin and chromogranin (data not shown). Laboratory tests diagnosed an acute flare-up of autoimmune haemolytic anaemia, due to the presence of anaemia, total bilirubin 4.58 mg/dl, direct bilirubinaemia 0.38 mg/dl and transferrin 183 mg/dl and haptoglobin was <15 mg/dl. due to the presence of anaemia, total bilirubin 4.58 mg/dl, direct bilirubinaemia 0.38 mg/dl, transferrin 183 mg/dl and haptoglobin was <15 mg/dl. The total reticulocyte count was 187.3 mil/ μ L, lactate dehydrogenase (LDH) 815 IU/mL and the anti-agglutinin test was positive (direct Combs 4+). The indirect Coombs' test was negative (-). IgG was 778 μ mol/L in the blood and cryoglobulins were negative. Due to this exacerbation of autoimmune haemolytic anaemia, surgery was delayed and corticosteroid treatment was started.

4.2. Evolution of Alpha-Fetoprotein

Among the blood parameters, a progressive increase in alpha-fetoprotein was observed from the onset of the disease, reaching 17.5 ng/ml in June 2020. In December 2023, in the acute phase of haemolytic anaemia it was 20.1 ng/ml and after surgical resection, in February 2024, it was 14.56 ng/ml. Six weeks after surgery, it was 18.2 ng/ml. (Table 1) shows the time course of haemocytometry, count and formula, platelets and total reticulocytes.

Table 1: Time course of blood parameters measured during the course of the disease, before and after surgery

Blood parameters	23-06-2020	14/12/2023 preoperative values. Episode autoimmune haemolytic anaemia	15-12-2023	18-12-2023	20-12-2023	29/01/2024 Day 1 surgical intervention. Post-surgical analysis	30/01/2024 Day 2 post-operative, morning	30/01/2024 Day 2 post-operative, afternoon	31/01/2024 Day 3 post-operative, morning	31/01/2024 Day 3 post-operative, afternoon	02-02-2024
Erythrocytes 10 ⁶ cells g/mL	4.66	3.1	2.88	3.11	3.03	3.37	3.34	2.76	2.74	2.83	3.22
Haemoglobin g/dL	14.4	11.3	10.3	10.3	10.1	10.4	10.6	8.5	8.7	8.6	9.9
Haematocrit %	41.8	30.9	27.7	29.9	29	30.8	30.3	26.2	25.7	26.5	29.8
Platelets mm ³	155000	138000	110000	115000	104000	119000	111000	119000	89000	87000	105000
Leucocyte 10 mm ³	6.13	7.8	3.6	3.9	4.8	24.2	17.9	26.3	10.2	11.5	8.8
Neutrophils 10 mm ³	2,734	5.69	2.26	2.24	2.93	20.76	15.13	19.99	8.43	8.26	6.98
Lymphocytes 10mm ³	2,611	1	0.73	0.78	0.67	0.51	0.36	0.79	0.72	0.72	0.77
Total Reticulocytes (mil/mL)	75.3		187.3		187.3				147.4	transfusion of 1 U hematies concentrate 2 U plasma 7 U platelets	

4.2. Imaging Tests

The patient underwent several imaging studies from the onset of the disease, which are shown in (Figure 1 (a), (b) and Figure 2 (a), (b)). In 2020, an abdominal CT scan was performed due to the presence of a cystic tumour in the right kidney, which turned out to be a renal cyst. At that time, the inter aorto-caval space showed no relevant findings, only a small nodular lesion ventral to the abdominal aorta and caudal to the third duodenal portion, which could be the origin of the tumour. Another CT scan was performed in 2022; showing a nodular image was detected of high attenuation with a less intense central enhancement area, the largest diameter of which was 2 cm. The differential diagnosis was adenopathy or paraganglioma: see (Figures 1(a) and (b)). In the same year, a PET scan was performed; it showed a 2 cm lesion of nodular morphology with mild metabolic activity (maximum SUV 2.2). In January 2023, a control abdominal CT scan showed a nodular image with a larger diameter of 2.34 cm. Six months later, an MRI was performed, in which a tumour compressing the anterior aspect of the cava measuring 2.7 cm x 2.3 x 3.4 cm was observed; The tumor was hyperintense in T2-weighted sequences, with heterogeneous enhancement after contrast administration. The diagnostic conclusion was of a retroperitoneal tumour, possibly paraganglioma.

See (Figure 2(a) and (b)). In April 2023, a sectorial and radial echo-endoscopy was performed, up to the second duodenal portion and distal to the papilla. A 2.5 cm rounded lesion was observed; it was well defined according to a pseudo-capsular image and shown to be heterogeneous via ultrasound and elastography, in intimate contact with the duodenal wall. FNA was performed in three passes with a 22 G needle and material was obtained for the impression and cytoblock. The cytological report described areas of necrosis within the tumour and the pathological anatomy described fibrin bands and a lymphopolynuclear infiltrate. No epithelial cell clusters were identified. (Table 2) The evolution of the tumour size and its cumulative density that are shown below (Figure 3). The findings reveal that the nodular lesion has increased in size over time. This shows the cumulative proportion of tumour sizes in the different measurements obtained in the imaging tests. The starting point corresponds to the smallest tumour size and the end of the histogram corresponds to the largest tumour size. The normal distribution function is shown in red. This was a nodular lesion, with increased proliferative activity and size; it was imprinting on the inferior vena cava and likely to increase in size in the coming months; thus, even without a precise diagnosis, it was indicated surgery.

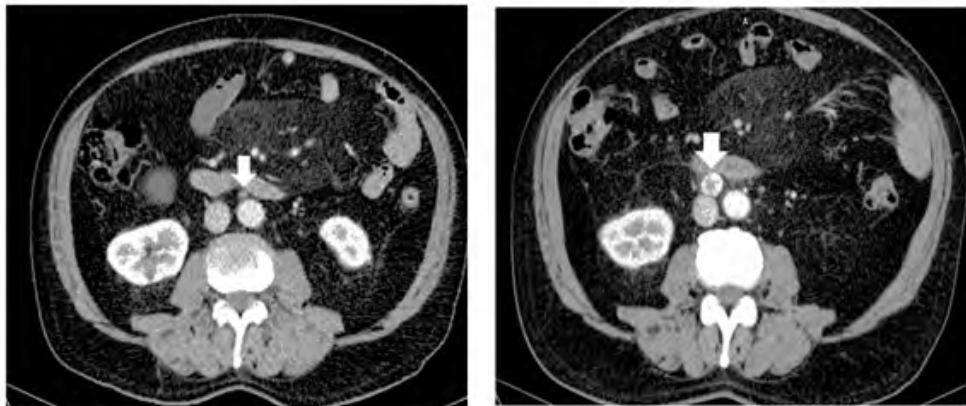


Figure 1: (a) Abdominal CT scan showing a full small nodule ventral to the abdominal aorta. (b) Two-centimetre-high attenuation nodular image, with a central area of slight staining. Both tumours are marked with a cross.



Figure 2: (c) Abdominal CT scan. Nodular full tumour of 2.34 cm. with high attenuation, with central Area of less staining. d) Abdominal MRI with enlargement of the inter aorto-caval tumour, which imprints on the anterior aspect of the cava.

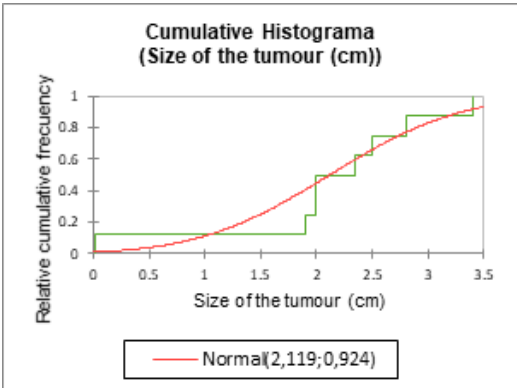


Figure 3: Cumulative histogram of the size tumour

Table 2: Evolution of the tumour size and transformation time series. Computed axial tomography (1), positron emission tomography (2), echoendoscopy (3), magnetic resonance imaging (4).

N° type of radiological and endoscopic examination	Diagnostic test	Date on which the test diganostic was performed	Size of the tumour cm.	Average number of days elapsed be- tween diagnostic tests
1	TAC	17-11-2020	0.01	0
1	TAC	04-02-2022	2	444
1	TAC	27-04-2022	1.9	59
2	PET	15-07-2022	2	79
1	TAC	30-09-2022	2.8	77
1	TAC	10-01-2023	2.34	102
3	Echo-endoscopy	13-04-2023	2.5	93
4	MRI	30-11-2023	3.4	231

4.3. Surgery

A median supra- and infra-umbilical incision was performed. The operative findings included epiploic adhesions to the gallbladder bed due to a previous cholecystectomy surgery, diverticular disease of the sigmoid colon, retractile mesenteritis, and fibrosis of Toldt's fascia, as well as a right renal cyst. In addition, an encapsulated tumour was identified between the aorta and the inferior vena cava, occupying the entire anterior aspect of the latter. The operation consisted of dissection of the right colon and terminal ileum from the lateral to medial positions, performing the Kocher manoeuvre. The lateral borders of the vena cava and the abdominal aorta were identified and dissected, as well as the third portion of the duodenum, the triangle in which the tumour was located. The tumour was resected in its entirety. The perioperative anatomopathological

analysis indicated a vascular tumour of undetermined malignancy. Haemostasis was performed and a haemostatic dressing (Surgicel) was placed on the anterior aspect of the vena cava. The dissection bed of the tumour was drained using a Jackson-Pratt surgical drain. Images of the operative field are shown in (Figures 4a and 4b). Serological types of autoimmune haemolytic anaemia include warm haemolytic anaemia, cold agglutinin disease (CAD), and a mixed type. In CAD, symptoms are associated with temperature fluctuations and rapid cooling that can lead to haemolysis [16]. For this reason, during the operation and the patient's stay in the intensive care unit, serum therapy was administered at a constant temperature, avoiding sudden changes in temperature, even though no circulating cryoglobulins were identified in the blood.

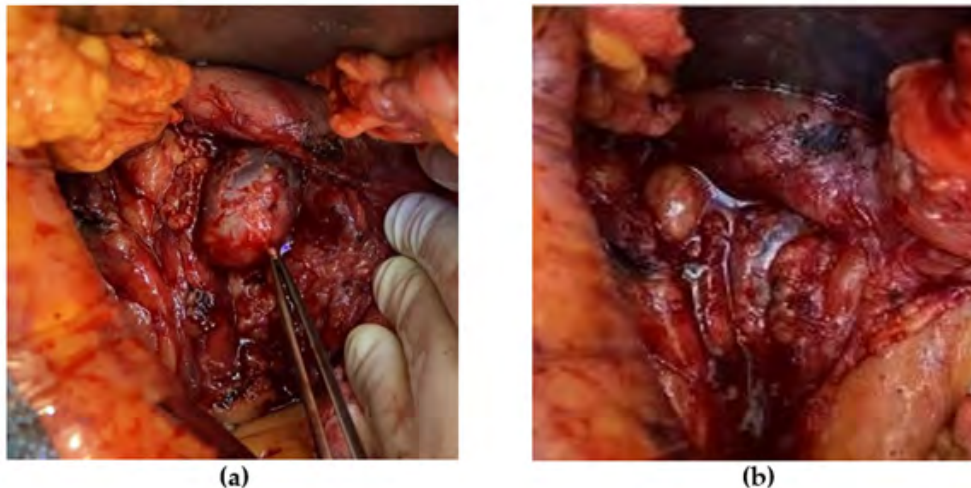


Figure 4: (a). Operative field. Retroperitoneal tumour caudal to the third duodenal portion and inter aorto cava. (b). Surgical resection bed, anterior aspect of the cava.

4.4. Clinical Evolution and Follow-up

Despite preventive treatment preventive corticosteroids, that started preoperatively and continued postoperatively, after three days of surgery, the patient presented anaemia, platelets, and elevated total reticulocytes. During this time, he maintained intra-abdominal aspiration drainage, showing no significant blood drainage. He received one unit of red cell concentrate, seven units of platelets, and two units of plasma. The patient experienced no new postoperative complications, resumed oral feeding on the third postoperative day and was discharged seven days after surgery.

4.5. Histopathological Examination

The histopathological examination revealed a macroscopically well-defined nodule measuring 3.7 x 2.5 x 2.2 cm. The cut surface of the nodule shows haematopoietic and myxoid areas (Figure 5). Using light microscopy, a medium-to-large vessel-associated growth pattern was observed, mainly at the periphery. The anas-

tomosing proliferation of capillary channels was prominent; the endothelial cells showed no cellular atypia and no multilayered pleomorphism. No mitoses were detected. There were frequent fibrin thrombi. Marked extramedullary haematopoiesis was evident with erythrocyte precursors and other cell types, including megakaryocytes. Within the lesion, foci of mature adipose tissue were found. The stroma exhibited areas of sclerosis, oedema, and myxoid changes, preferentially in the central region. Based on immunohistochemistry, the vascular channels of the tumour were found to express high levels of CD31 and CD34. Smooth muscle actin was not detected in the endothelial cells but was observed in the vascular wall, with a support network enhanced by benign pericytes. The rate of Ki-67 proliferative activity in the tumour was very low, with marked expression in the haematopoietic component. The alpha-fetoprotein test was negative. The microscopic features of the tumour can be seen, in (Figure 6 (a-f)), with their corresponding magnifications.

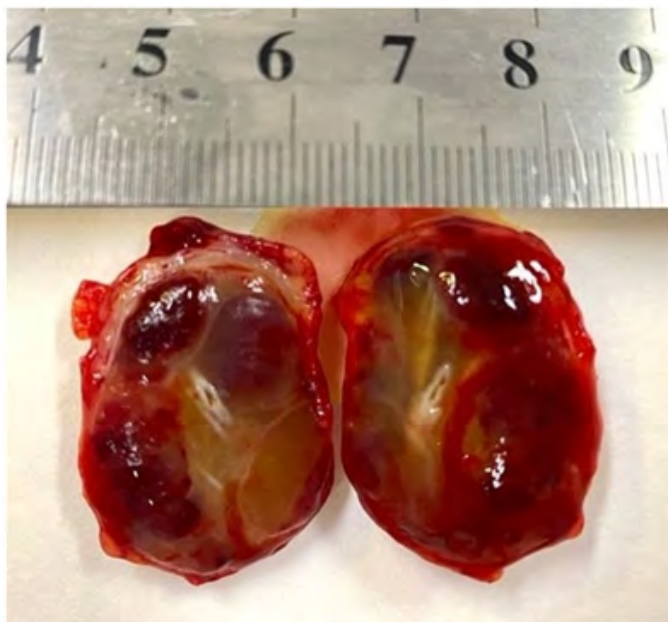


Figure 5: Macroscopic anatomy: anastomosing haemangioma.

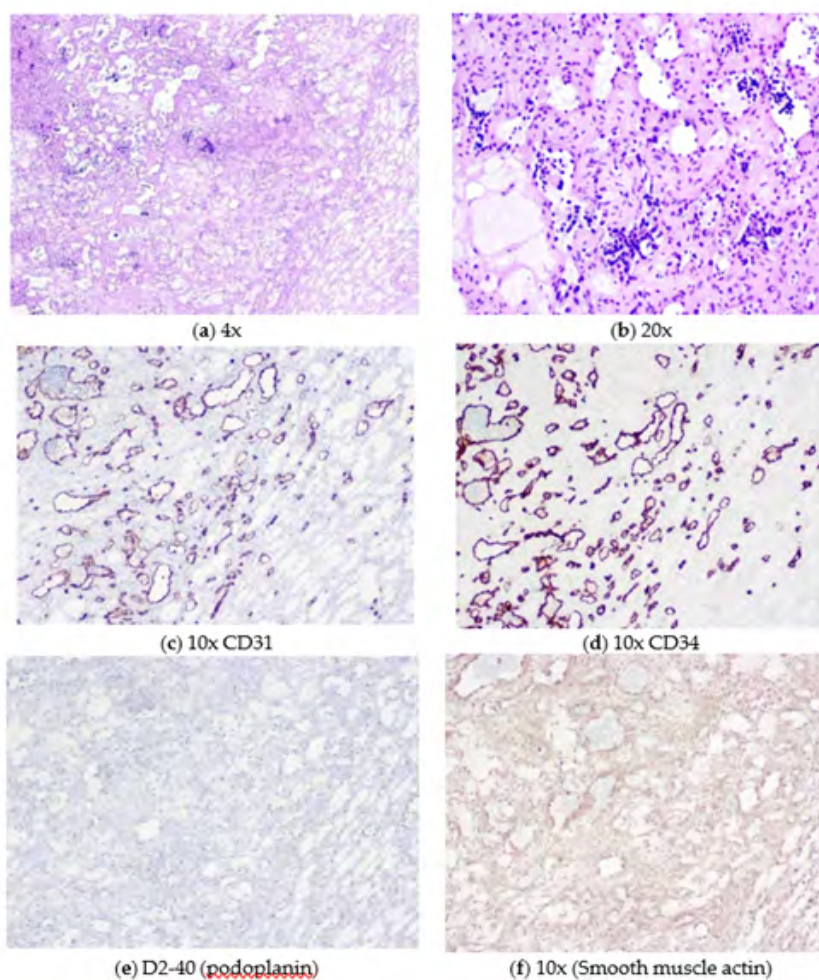


Figure 6: (a) Thin-walled anastomotic channels lined by a monolayer of endothelial cells. (b) Injuries to the endothelial cells are small. There are foci of extra-medullary haematopoiesis within the vascular channels. Erythrocyte precursors and megakaryocytes are seen. (c), (d), and (e) Expression of endothelial markers. Lesional channels express high levels of CD31 (c) and CD34 (d) whereas the expression of D2-40 (podoplanin) (e) is negative. (f) Smooth muscle actin expression is negative in endothelial cells but is positive in the pericyte support network.

5. Discussion

5.1. Radiological Features of Anastomosing Haemangioma and the Differential Diagnosis

Well-defined hyperintensity or isointensity in the genitourinary tract tumours on T2 WI and progressive vascular enhancement patterns by MRI and CT, are diagnostic features of anastomosing haemangioma [17]. In addition, they include the morphological features of the tumour, clear borders, density, and heterogeneous signals, with apparent enhancement, which are similar to those of extra-adrenal paraganglioma. Both processes are richly vascularised. In our case, a functional hormonal study of the tumour showed no activity.

5.2. Indication for the Surgical Resection of the Anastomotic Haemangioma

Progressive tumour growth over time has been used as a guide for surgery. The average size of an anastomosing haemangioma is 2.6 cm for non-renal haemangiomas [18]. As described in the results, the anastomotic haemangioma cell types analysed above show low mitotic activity in the tumour, based on Ki-67 expression and an SUV of 2.2 on the PET, which do not explain the increase in tumour size over time. However, the growth of the anastomosing haemangioma may be explained by the increased proliferative activity of the haematopoietic tissue, as demonstrated by the expression of Ki-67 in this tissue. As discussed below another possible cause of increased tumour size is PDGF (platelet-derived growth factor), which activates the MAPK cell signalling pathway. This pathway is involved in the regulation of cellular functions including proliferation, cell survival, inflammation, and apoptosis in response to various stimuli [15]. This may be one of the pathways used by the anastomosing haemangioma, accounting for the increased tumour size, as well as for the fact that areas of central cell necrosis appear in a biopsy undertaken via endoscopic ultrasound and imaging. However, this has not been evaluated in this case.

5.3. Surgery

The resection of both the aorta and inferior vena cava (IVC) is a surgical procedure that requires both favourable tumour biology and a patient suitable for this type of surgery; however, resection offers the possibility of a cure [19]. The absence of infiltration of the anastomotic haemangioma on the anterior aspect of the cava allowed for the resection of the tumour, without the resection of the cava.

5.4. Fibroblast Reprogramming and Angiogenesis

Several studies have described the existence of small colonies of progenitor cells at various sites in the arterial wall, especially in the adventitia [20]. These progenitor cells include endothelial, smooth muscle, and haematopoietic stem/progenitor cells [21]. The adventitia of the abdominal aorta can release platelet-derived growth factor (PDGF) and transforming growth factor-beta 1 (TGF- β 1) to recruit mesenchymal cells from the bone marrow

and circulation [22]. PDGF is also a mitogen and chemoattractant that alters vascular homeostasis by inducing inflammation, oxidative stress, and phenotypic transition. Elevated PDGF levels during the proliferative phase can cause endothelial cells to proliferate while inhibiting adipocyte differentiation. The change in cell composition in the haemangioma during the involutive phase may indirectly lead to a reduction in PDGF- β content and trigger adipocyte differentiation [23]. Fibroblast reprogramming plays an important role in angiogenesis. Adult fibroblasts can be converted into progenitor cells and even different types of endothelial cells required for blood vessel formation. The presence of a high density of co-transplanted fibroblasts is an important factor in angiogenesis [24]. The nodular image ventral to the abdominal aorta on the 2020 CT scan could correspond to these small colonies of progenitor cells, which would represent the beginning of the anastomosing haemangioma.

5.5. Angiogenesis in Anastomotic Haemangioma

Angiogenesis is a key component in the biology of haemangiomas, especially during their growth phase. When the tumour expresses CD31-CD34-type endothelial markers, it indicates angiogenic activity within the tumour. Vascular tumours that over-express PDGFR- (platelet-derived growth factor receptor β) can stimulate platelet production and angiogenesis by promoting the formation of new blood vessels and early haematopoiesis [14]. Vascular mimicry-positive tumour cells recruit pericytes to facilitate germination and provide structural support for vascular-like networks. Pericyte recruitment is mediated by platelet-derived growth factor (PDGF- β) [25]. In the anatomo-pathological study of the anastomosing haemangioma, we observed megakaryocytes in the tumour and the enhancement of the benign pericyte support network. Therefore, it could be suggested that PDGF played a role in this development. In addition, the appearance of platelets three days postoperatively could be explained by the removal of the tumour and the cessation of the stimulation of platelet production by PDGF. Consequently, PDGF- β signalling could have been prevented by blocking PDGF receptors with a tyrosine kinase inhibitor or by blocking antibodies that inhibit vascular mimicry and tumour growth [23].

5.6. Other Phenotypic Transformation of Mesenchymal Cells

Regarding the phenotypic transformation of vascular smooth muscle cells (VSMC), PDGFs bind to PDGFRs and block the synthesis of contractile VSMC marker proteins, such as alpha-smooth muscle actin (α -SMA) and smooth muscle myosin heavy chains [26]. This could explain why, based on immunohistochemistry, we did not observe the expression of the smooth muscle alpha-actin antibody (α -SMA) in endothelial cells or in smooth muscle fibres, but in the pericytes of the anastomosing haemangioma.

5.7. Alpha-Fetoprotein

In anastomosing haemangioma, immunohistochemical expres-

sion of alpha-fetoprotein in tumour tissue is negative; therefore, we speculate that elevated serum levels of alpha-fetoprotein are indirectly caused by anastomosing haemangioma. This same mechanism has already been proposed for infantile haemangioma [27]. Interaction between the anastomosed haemangioma, possibly derived from the mesoderm of the abdominal aortic adventitia, fibroblastic reprogramming and endogenous endodermal liver tissue in the vicinity of the tumour portal drainage results in the production of alpha-fetoprotein by the liver. This approach explains the decrease in the level of alpha-feto protein in the immediate postoperative period after complete tumour resection, while it does not explain the increase in its level weeks after surgery.

5.8. Characteristics of Erythrocyte Differentiation in Bone Marrow (erythroblastic islands) and Extra-Medullary Haematopoiesis in Anastomosing Haemangioma

A feature of the process of erythrocyte differentiation or terminal maturation is that it takes place in anatomical niches, known as erythroblast islands; these are unique to mammalian erythropoiesis and are preferentially located in the bone marrow [28]. Erythroblast islands consist of macrophages surrounded by about thirty erythroid cells of varying degrees of maturation. The main growth factors that regulate erythropoiesis in vivo are stem cell factors, granulocyte colony-stimulating factors, interleukins IL-3, IL-6, and IL-11, and erythropoietin. TGF- β 1 accelerates terminal erythroid differentiation by delaying cells in the G1 phase [29]. However, extra-medullary haematopoiesis has been observed in the anastomosing haemangioma analysed. The structures formed at this level are similar to erythroblastic islands, but extramedullary haematopoiesis encompasses a wider range of maturing cell types such as erythrocyte and megakaryocyte precursors. This pathological or compensatory process is described in response to certain clinical conditions as anaemia.

5.9. Autoimmune Haemolytic Anaemia: Mutations of Clonal Haematopoiesis

Autoimmune haemolytic anaemia is mediated by autoantibodies and/or complement together with activated macrophages, T-lymphocytes and cytokines such as IL-6, which contribute to the process directed against red blood cells to cause premature erythrocyte destruction. All these immune parameters change with age, and immunosenescence is a mechanism associated with autoimmunity [30]. In most cases of autoimmune haemolytic anaemia, there is no clonal disease with erythropoietic proliferation in the bone marrow. This phenomenon only occurs if there are somatic mutations in the erythroid progenitor cells. Mutated genes used to define clonal expansions of haematopoietic cells include DNMT3A (DNA protein (cytosine-5)-methyltransferase 3A), TET2 (protein methylcytosine dioxygenase), JAK2 (tyrosine-protein kinase) and SF3B1 (splicing factor 3B subunit 1). These genes are mutated in chronic myeloid leukaemia and myelodysplastic syn-

dromes, which are clonal haematopoietic disorders characterised by ineffective haematopoiesis and peripheral blood cytopenias. Therefore, it would not be surprising if these tumours could develop from erythropoietic clones. However, these mutations are also present in the elderly population. In conclusion, erythropoietic clonal proliferation in anastomosing haemangioma may be secondary to autoimmune haemolytic anaemia and compensates for the loss of red blood cells in bone marrow affected by senescence. The prognosis of anastomosing haemangioma is good; the islands of erythroblasts observed in the tumour periphery and the clonal expansions of viable red blood cells could be beneficial to the patient's autoimmune haemolytic anaemia. However, since these mutated genes are present in haematological neoplastic processes, the removal of the tumour should be considered. Therefore, a possible causal relationship between autoimmune haemolytic anaemia and anastomosing haemangioma is proposed. Future lines of research should aim to create sustainable research infrastructures that facilitate the collection of tissue and liquid biopsies, together with clinical and biological data from these tumours, as proposed by the clinical and translational research of the international malignant germ cell consortium [31].

6. Author Contributions

Conceptualization, J.L. and I.L.; methodology, J.L. and E.I.; software, J.L., E.I.; resources, A.S. and I.S. and B.M.; data curation, J.L. and E.I.; writing—original draft preparation, J.L.; writing—review and editing, E.I. and I.L.; visualization, J.L. and A.S. and I.S. and E.I. and B.M.; supervision, I.L. and E.I. All authors have read and agreed to the published version of the manuscript.

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8. Institutional Review Board Statement

While no IRB was required for this study, acquisition, storage, photography, and disposal of all tissues conformed with ethical and biosafety considerations. Informed Consent Statement: The patient gave informed consent prior to surgery.

9. Data Availability Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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11. Conflicts of Interest

The authors declare no conflicts of interest.

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