Orthotopic Liver Transplantation for Hereditary Hemorrhagic Telangiectasia and MEN Type I Syndrome – Case Report and Review of Literature

Mihnea-Ioan Ionescu, Ian David Edwin Nesbitt, Colin Hugh Wilson, Samantha Erica Saikia, David Talbot

1Liver Unit, Queen Elizabeth Hospital Birmingham, University Hospitals, Birmingham NHS Foundation Trust, United Kingdom
2Department of Perioperative and Critical Care, Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust, United Kingdom
3Department of Hepatobiliary and Transplant Surgery, Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust, United Kingdom
4Department of Radiology, Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust, United Kingdom

Abstract

Trasplant hepatic ortotopic pentru telangiectazie hemoragică ereditară asociată cu sindromul neoplaziei endocrine multiple (MEN) Tip I – prezentare de caz și review al literaturii

Introduction: Telangiectazia hemoragică ereditară (THE) este o maladie genetica rară moștenită autozomal dominant, caracterizată prin malformații arterio-venoase (MAV) care afectează în principal plămânii și ficatul. În cazul prezentat gravitatea MAV a condus la ciroză hepatică decompensată, ceea ce a impus ulterior transplantul hepatic (TH).

Prezentare de caz: Un pacient de sex bărbătesc, în vârstă de 59 de ani, care fusese diagnosticat în prealabil cu sindrom de neoplazie endocrină multiple tip 1 (MEN 1), a fost inclus pe lista de aşteptare pentru TH, indicaţia constând în hepatopatie în stadiu terminal, provocată de MAV hepatic. În cursul transplantului hepatic, dată fiind discrepanța marcată între diametrul arterei hepatiche la primitor versus donator, s-a decis efectuarea unei anastomoze arteriale latero-terminale. Posttransplant grefa hepatică a funcționat normal iar studiile echografice Doppler serieate au demonstrat o anastomoză arterială normală din punct de vedere morfologic și funcțional. Pacientul a decesat însă în ziua postoperatorie 39 datorită unei cauze independente (stop cardiac neresponsiv la manevrele de resuscitare în urma unui infarct miocardic acut).

Concluzii: Particularitatea prezentării constă în faptul că pacientul reprezintă primul caz de asociere între MEN tip 1 și THE raportat.
Introduction

Hereditary haemorrhagic telangiectasia (HHT), or Rendu-Weber-Osler disease, is a genetic disease transmitted in an autosomal dominant (heterozygous) manner (1), characterised by vascular abnormalities of either small size (telangiectasias) or large size arteriovenous malformations (AVMs). The homozygous form has been proven to be lethal (2). The disease was first reported by Babinton in 1865, then by Rendu in 1896, Osler in 1901, and Weber in 1907; each reported the disease, which was named Osler-Weber-Rendu disease. Since then Hanes has coined the term ‘hereditary haemorrhagic telangiectasia’ (3).

HHT is considered a rare disease (1:5000) (4), with no significant difference regarding gender or race (5). The highest prevalence has been observed in Europe, on the Danish island of Fyn and in the French departments Ain, Deux-Sevres and Jura (6).

Abstract

Introduction: Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant genetic disorder characterized by arteriovenous malformations (AVMs) mainly affecting the lungs and the liver. In this case AVM’s resulted in liver cirrhosis and an indication for orthotopic liver transplantation (OLT).

Case Report: A 59 year-old male patient with HHT who had been previously diagnosed with Multiple Endocrine Neoplasia type 1 Syndrome (MEN 1) was listed for OLT for end-stage liver disease due to hepatic AVMs. During the procedure, a novel type of arterial anastomosis (end-to-side) was chosen because of the mismatch in diameter between the hepatic artery (HA) of the donor and the recipient, respectively. Graft function was normal and repeat Doppler ultrasound studies showed a normally functioning arterial anastomosis. However, the patient died on POD 34 due to an unrelated cause (cardiac arrest resulting from myocardial infarction).

Conclusion: To the best of our knowledge this is the first report of an association of HHT and MEN 1. Moreover, this is also the first reported end-to-side arterial anastomosis in an HHT patient during OLT. Our paper shows that the surgical technique we applied is both feasible and safe.

Key words: hereditary haemorrhagic telangiectasia, multiple endocrine neoplasia syndrome type 1, orthotopic liver transplantation
venous malformations in the liver can progress to end-stage liver disease through various mechanisms, which in turn may necessitate liver transplantation.

We report a case of HHT occurring in a patient with a history of Multiple Endocrine Neoplasia type 1 syndrome (MEN 1), who received an orthotopic liver transplantation with a novel technique of performing the arterial anastomosis.

To the best of our knowledge, the case we report is the first association of HHT and MEN 1 in the world. Moreover, the type of arterial anastomosis (end-to-side, with intact stumps of the gastroduodenal and splenic arteries), has not yet been reported in this situation.

Case Report

The patient, a 59 year-old male, developed recurrent epistaxis. His personal history included multiple endocrine neoplasia type 1, including a previous GH-secreting pituitary tumour for which he underwent a transcranial resection and radiotherapy. After this he developed a mild overall hypopituitarism and was started on low doses of L-thyroxine. He had also developed hyperparathyroidism for which he had a parathyroidectomy. His family history was unremarkable.

A computed tomography (CT) scan noted at least 4 pulmonary arteriovenous malformations (PAVMs) (Fig. 1). The largest one, located in his left upper lobe, had an 8 mm feeding vessel (Fig. 2). However, an angiogram showed no left upper lobe pulmonary AVM, but a small right sided pulmonary AVM considered not significant enough to be embolised.

Moreover, the patient had multiple hepatic AVMs. He did not develop portal hypertension, but he had mild cholestasis and moderate dilatation of his intrahepatic bile ducts as shown by magnetic resonance imaging (MRI) (Fig. 3). Thus he was diagnosed with hereditary haemorrhagic telangiectasia, having a Curacao score of 2.

Gradually, the patient also developed breathlessness to exercise. No evidence of pulmonary hypertension was discovered on
cardiac catheter (October 2012): mean pulmonary pressure of 21 mmHg, right atrial pressure of 8 mmHg and pulmonary capillary wedge pressure of 13 mmHg). He had a high cardiac output at 15.3 L/min (normal range 4.0 - 8.0 L/min, a cardiac index of 7.64 L/min/m² and a normal pulmonary vascular resistance at 47 dynes. Therefore this symptom was attributed to high-output cardiac failure (HOCF).

The coeliac axis is grossly dilated and very tortuous, with the common HA, measuring 2.5 cm in diameter (Fig. 4).

Due to the fact that his high output cardiac failure progressed, the patient was assessed for liver transplantation. While on the transplant list, he developed atrial fibrillation, which was controlled with bisoprolol, as well as a transient ischaemic event manifest with upper limb paresthesia. No AVMs were noted in his brain.

The echocardiography performed as part of his pretransplant assessment revealed normal left and right ventricle size and thickness, and normal left ventricular systolic function; ejection fraction by visual estimate was 50-55%. The patient had mild tricuspid regurgitation and a pulmonary artery (PA) systolic pressure of 37 mmHg. The pulmonary hemodynamic study showed, in addition to increased mean PA pressure, elevated pulmonary vascular resistance and a PA occlusion pressure < 15 mmHg, ruling out the presence of hyperdynamic and/or hyperkinetic portal hypertension.

His liver function as well as his HOCF worsened to the point where he was assessed and listed for cadaveric liver transplantation in 2015. Both systemic treatment with bevacizumab and HA embolization were considered; however, due to the high rate of side effects of these approaches, they were not undertaken.

Whole organ donor after brain stem death (DBD) orthotopic liver transplantation was performed in February 2017. Intraoperatively, due to the significant mismatch in calibres between the donor and the recipient hepatic arteries, the unusual decision was made to perform an end-to-side arterial anastomosis, with continuous 5-0 Prolene sutures (Fig. 5), primarily to deal with the size discrepancy between the 2 vessels.

Postoperative doppler ultrasound of the graft showed patent portal vein and hepatic veins with normal directional flow and a patent, pulsatile hepatic artery.

The patient’s liver function gradually normalised. He was weaned from ventilation support. However, he developed significant hypoxemia. Emergency arteriography of his lungs revealed no significant modification in arterial blood gases when his PAVM was occluded; therefore it was decided not to embolize it. His hypoxemia progressively improved until complete resolution following ventilation in a prone position.

The patient’s overall status significantly improved but unfortunately on postoperative day 34 he suffered a sudden acute myocardial infarction and died, despite resuscitative attempts in the critical care facility.

Discussion

Establishing a diagnosis of HHT depends on the Curaçao criteria: at least 2 of the following indicate a positive diagnosis: i. “hereditary” (dominant familial aggregation) - at least one first degree relative affected by HHT; ii “haemorrhagic” – spontaneous, recurrent epistaxis; iii. “telangiectasia” - several concentrated lesions, never diffuse, at typical sites, in

Figure 4. Hepatic arteriomegaly (2.5 cm diameter) (arrow)
Orthotopic Liver Transplantation for Hereditary Hemorrhagic Telangiectasia and MEN Type I Syndrome – Case Report and Review of Literature

the following descending order: nasal mucosa, oral mucosa, facial skin and fingertip pulps; iv AVMs – pulmonary, cerebral, hepatic, spinal (13) and pancreatic (14). A history of 1 criterion makes the diagnosis ‘unlikely’, 2 criteria make the diagnosis of HHT ‘possible’, while 3 of them make it ‘definitive’ (15).

The most frequent underlying genetic mechanisms of HHT pathogenesis consist of inactivating mutations of endoglin (causing HHT type 1), and ALK-1 (determining HHT type 2), respectively (16).

The first liver transplantation for HHT was reported in English literature in 1995 (17), and since then it has become a well-established procedure. The largest series (44 patients) was reported by Lerut et al (6) in 2006. It is a challenging procedure, due to major blood loss and subsequently longer hospital stay (10).

Careful assessment of the liver transplant (LTx) potential recipients has to be performed before the actual surgical procedure. Particularly, their hepatic AVMs (HAVMs) as well as any coexisting pulmonary AVMs (PAVMs) need thorough characterization. The multidisciplinary team needs to make sure that no other available medical/surgical or interventional treatment would give the patient a greater benefit before / on lieu of LTx.

**Pathogenesis of HHT**

The pathogenesis of HHT is triggered by mutations in one the following genes involved in the TGF-β (transforming growth factor-beta) signalling pathway: i. ENG (chromosome 9q34) (Online Mendelian Inheritance in Man – OMIM gene description reference 131195) which encodes the endoglin protein and is associated with HHT type 1; ii. Activin A receptor type II-like 1 (ACVRL on chromosome 12q13) (OMIM 601284), which encodes the ALK-1 protein) and is associated with HHT type 2; iii. MADH 4, situated on chromosome 18q21 (OMIM 600993), which encodes

---

**Figure 5.** The arterial anastomosis (vertical arrow) between the donor common hepatic artery (slim horizontal arrow) and the recipient hepatic artery, in an end-to-side manner. The fat horizontal arrow marks the stump of the hepatic artery.
the SMAD 4 protein (18) and causes HHT – juvenile polyposis syndrome. Cases of concomitant mutations of ENG and ACVRL, as well as mosaicism of ENG have been reported (19). The aforementioned genes are responsible for modulating the formation of the intima and when they are mutated, this process takes place in an aberrant manner, giving rise to AVMs. Together they are responsible for more than 98% of the cases of HHT (20).

Other genetic factors involved in the pathogenesis of HHT are the bone morphogenetic protein (BMP) mutations, which are responsible for less than 1% of the HHT cases (21). BMP 9 (OMIM605120) and BMP 10 (OMIM 608748), which are present in blood, bind to both endoglin and ALK-1 on endothelial cells and induce angiogenetic quiescence. If either endoglin or ALK-1 is mutated, signalling through this pathway decreases and a strong angiogenetic answer is elicited (22).

However, clinical manifestations of HHT can be present in patients who test negative for mutations in these three genes, indicating other genes may be involved (23).

The ALK-1 mutation predominates in HHT patients from Mediterranean countries (Spain, France, Italy), and it correlates with higher frequency of HAVMs and a later onset (HHT-2) (24). This mutation has nevertheless been reported in neonates with HHT-associated HOCF (25). On the other hand, endoglin mutation occurs more frequently in patients from North America and Northern Europe and is correlated with severe, early clinical manifestations and more frequent PAVMs and cerebral vascular malformations (HHT-1) (24). However it is unclear if this reflects genuine geographic variance or referral practice (26).

HHT displays significant phenotypic variability, wherein the location and number of AVMs and telangiectasias can vary widely even between members of the same family. This is not due to genetic heterogeneity: rather, the intra-familial phenotypic variation may be explained by the effect of 2 genetic modifiers: PTPN14 (protein-tyrosine phosphatase, non-receptor-type, 14: OMIM 603155) and ADAM17 (a disintegrin and metalloproteinase domain 17; OMIM 603639); these 2 genes can also influence the severity of clinical manifestations of HHT (27).

**Hepatic Arteriovenous Malformations**

The most common cause of diffuse vascular malformations in the liver is HHT (28). Although a majority of HHT patients display liver AVMs (29), only 8% of these ever become clinically manifest (5). Hepatic arteriovenous malformations (HAVMs) are predominantly seen in HHT type 2 and classically manifest in either of the following ways: HOCF (most frequently) (30), biliary sepsis or portal hypertension.

The pathological mechanism of HAVMs in HHT is triggered by the opening of the arteriovenous fistulas, which causes a decrease in arterial pressure as blood shifts to the venous system. This in turn increases the cardiac output and is further exacerbated by the iron deficiency anaemia associated with bleeding telangiectatic lesions (31). The physiologic corollary is a decrease in left ventricular after load and venous resistance, which activate the sympathetic system and the consequent increase in heart rate and resulting hyper-dynamic circulation (32). Irreversible pulmonary hypertension, a potential contraindication for LTx might ensue: therefore, LTx must be performed before irreversible pulmonary hypertension develops (33).

There are 3 types of HAVMs: arterio-caval (the most frequent by far): arterio-portal and porto-caval. Arterio-caval shunts are responsible for the most serious and the most frequent complication of HHT, high output cardiac failure (HOCF). Arterio-portal shunts lead to ischemic periportal fibrosis and portal hypertension. Porto-caval shunts cause portosystemic encephalopathy (34), but so far they have been only demonstrated at necropsy or on vascular corrosion castings.

Arterio-portal shunts lead to particularly serious complications, as the resultant portal hypertension due to the increased blood inflow determines increased deposition of fibrin. This in turn causes an increased nodularity of the
liver, with the development of ‘pseudocirrhosis’ (35). Pseudocirrhosis is also determined by ischemia-induced regenerative nodular-like formation, provoked by a lack of normal arterial inflow in the liver, as well as by the development of heart failure (36). The most frequent type of liver parenchymal remodelling in HAVMs is focal nodular hyperplasia (6).

A wide spectrum of clinical manifestations associated with HHT has been described. This case report presents some interesting features regarding the pathophysiology of HHT and the clinical decision-making process in the treatment of these patients.

**Pulmonary Arteriovenous Malformations**

PAVMs are abnormal communications between pulmonary arteries and pulmonary veins, without the interposition of a capillary bed. They are usually multiple, bilateral and tend to be located at the pulmonary bases (37). PAVMs can be either discrete or diffuse; the latter are defined by involvement of all segmental or subsegmental arteries of at least one lobe (38). Depending on the number of arteries feeding the PAVM, there can be either simple (1 vessel), or complex (multiple feeding arteries) PAVMs (39).

Pulmonary arteriovenous malformations (PAVMs) occur in 50-63 % of patients with HHT (40), and tend to be associated with HHT-1, rather than HHT-2 (41). 80-90% of the patients who have pulmonary PAVMs have HHT (42). They occur in approximately 37% of the patients with hepatic HHT, while brain AVMs were noted in only 10% (43).

PAVMs expose HHT patients to a wide range of potential complications caused by the right-to-left shunt: transient ischemic attack (10%), stroke (10-19%), hypoxemia, air embolism and secondary polycythemia and brain abscess (5-19%) (44). This is caused by septic emboli in the deoxygenated blood entering the brain via paradoxical embolism (45). It is noteworthy that neurological manifestations are more common in those with pulmonary arteriovenous fistula (AVF) than in those with cerebrovascular malformations. A wide majority (80-90%) of all PAVMs appear in patients with HHT. Only about a third of PAVMs are clinically manifest (dyspnœa, platypnea and haemoptysis) (46).

Therefore it is extremely beneficial to screen patients with HHT for PAVMs, either with transthoracic echocardiography with agitated saline or with chest CT. A recent study involving a significant number of the HHT Centres of Excellence throughout the world has shown a tendency for combining the two methods in a stepwise approach: repeat echocardiogram is followed by contrast-enhanced CT in order to discern between false-positive cases and true PAVMs (47).

Due to its safety and efficiency, percutaneous transcatheter embolisation of PAVMs has become the gold standard treatment (48). This procedure is efficient and durable in 83% of patients (49). Embolization is recommended in patients with HHT whenever PAVMs accessible to the procedure are found, even in asymptomatic patients (50), especially when the diameter of the feeding vessel is > 3 mm. A majority of centres treat PAVMs with a feeding artery < 3 mm.

Follow-up with CT is required every year in subsegmental diffuse PAVMs types, and every 5 years in the other cases, because of the risk of PAVM recanalization or regrowth of untreated ones (51).

Our patient had multiple PAVM that were not considered significant enough to be embolised prior to the transplantation. After the LTx, significant hypoxemia mandated a trial balloon occlusion of the largest PAVM in our patient. However, this did not improve the patient’s status. This was presumed to be due to atelectasias of the lung bases: the patient’s respiratory status improved continuously until he was completely weaned off respiratory support by intermittent ventilation in a prone position.

Patients with recurrent ischemic complications caused by paradoxical embolization related to PAVMs should be considered for VATS resection, especially if the lesions display a subpleural location (52). However, there is inconsistency in the screening, treatment and follow-up of PAVMs, which mandates further research and guideline development.
Patients with worsening PAVMs despite repeat embolization, or those with diffuse disease, should be considered as candidates for lung transplantation for their pulmonary disease (53). Fukushima et al (54) reported that lung transplantation in the setting of diffuse lung PAVMs transplantation may contribute to a reduction of AVMs in other organs and decrease the risk of vital complications, such as brain haemorrhage.

Central Nervous System AVMs

AVMs of the central nervous system in HHT patients are not considered to be congenital; rather, they are thought to develop in infancy, during the continuous development of arteriovenous maturation. Spinal AVMs occur more frequently in the thoracic spine and are always perimedullary; the preferred therapeutic approach is percutaneous coil embolization (55).

There are 3 subtypes of brain AVMs in patients with HHT: capillary AVMs, which do not have a shunt, direct arterio-venous communication (i.e. fistulous) or through a network (nidus) (56). Although it is generally considered that AVMs in the setting of HHT are congenital, a recent report documented a de novo brain AVM (57). Even though the risk of bleeding of brain AVMs has been found to be lower in comparison to sporadic AVMs, there have been reports of subdural hematoma as a presenting symptom of HHT (58).

Ocular manifestations of HHT have been reported, which include conjunctival and retinal telangiectasias and recently described choriocapillarisatrophy (59).

Other clinical manifestations of HHT include hemoptysis, melena, hematuria, and hypermenorrhea (60).

More recently, hyperandrogenemia due to impaired sulfonation of dehydroepiandrosterone as a result of portocaval shunting has been described in a young girl (61).

Rare associations of HHT have also been reported: hereditary angioedema (62), coronary embolisms as first manifestation of a PAVM (63), interstitial lung disease (64), rheumatoid arthritis with lung involvement (65), primary biliary cirrhosis (66), hepatocellular carcinoma (67), focal peliosis hepatis (68), Ebstein’s anomaly (69) and hypogonadotropic hypo-gonadism (70).

Patients with HHT have an increased risk of infections (brain abscesses), which cannot be explained solely by the paradoxical embolisms associated with PAVMs or by prolonged nasal packing for epistaxis. One possible explanation might be related to the fact that endoglin and, to a lesser extent, ALK1 are expressed by lymphocytes and mononuclear cells. Consequently, patients with HHT have a series of immunological abnormalities, including increased levels of immunoglobulins G and A, as well as T CD4, T CD8 and NK cell lymphocytopenia (71).

Lymphocytopenia seems to be linked to iron status and does not influence the risk of infection.

Cancer and HHT

Mutations in the endoglin, ACVRL-1 and SMAD4 genes alter the TGFβ pathway, which is responsible for angiogenesis. It can be speculated that reduced levels of endoglin could entail reduced angiogenesis in malignant tumours, therefore presumably influencing the progression of cancer. However, a recent Danish study has revealed that while HHT patients had a significantly lower prevalence of cancer, survival was similar to controls (72).

Liver Transplantation for HHT

Liver transplantation represents the best chance for the complete resolution of hepatic symptoms. Nevertheless, relapse of intrahepatic lesions posttransplantation have been reported (73). Even though it is difficult to distinguish between true recurrent HAVMs and peliosis (74), patients with HHT who have received a liver graft should benefit from regular long-term imagistic follow up.

The important enlargement of the coeliac trunk (75) poses specifically challenging technical problems to the surgeons, not least because the enlarged hepatic artery develops numerous anastomoses with the liver itself,
which dramatically increases bleeding during the explant.

Apparently the diameter of the splenic artery is proportionately less enlarged compared to that of the hepatic artery and the coeliac trunk. That is why some authors have selected the stump of the splenic artery as the recipient anastomotic partner of the arterial anastomosis during LTx (76). We performed an end-to-side arterial anastomosis because the operating surgeon considered a perfect match between the calibres of the anastomotic partners could be created.

Since most HHT patients who receive a liver graft preserve a good liver function, the main indication for LTx is HOCF. Therefore Model for End-Stage Liver Disease (MELD) exception points attributable to HHT patients seem the reasonable approach for this situation. Even though currently there are no formal recommendations for MELD exception points to be attributed to HHT patients a MELD exception score of 22 to treat high output cardiac failure as per the recommendation of the MELD exception Study Group can be requested (77).

Recently, various approaches of the HAVMs have been proposed, with various outcomes: percutaneous embolization or surgical ligation of intrahepatic shunts and systemic bevacizumab. Bevacizumab, a monoclonal anti-VEGF antibody, has been shown to reduce the severity of epistaxis (78), improve haemoglobin levels and reduce the necessity for blood transfusions in HHT patients; it improves cardiac output (30) and decreases HAVMs (62). Moreover, bevacizumab has been successfully used for stopping recurring gastrointestinal bleeding, repeatedly treated endoscopically (79). It also obviated the need for liver transplantation during a short term follow up (1 year) by reversing ischemic cholangiopathic lesions (80).

Nevertheless, it carries a significant risk of toxicity and may influence wound and anastomotic healing in OLT recipients, therefore it is not recommended as a bridging therapy for OLT (81). Some groups have even reported serious, life-threatening side-effects; therefore caution is advised when considering the use of bevacizumab (82).

Hepatic artery embolization (HAE) for HAVMs carries a satisfactory clinical response at long-term follow-up; however, the morbidity and mortality rate are comparable to LTx (83). Therefore, HAE should be only considered in HAVMs in patients who do not have concomitant portal hypertension, cirrhosis with encephalopathy, or pulmonary hypertension and cardiac failure, as this latter group of patients would obviously benefit from LTx rather than percutaneous treatment.

Ozawa et al have described a successful technique of open surgical repair of a hepatic artery aneurysm which improved the patient’s liver function (84).

A useful tool for predicting adverse outcome in adult patients, the HHT-score, has been devised by Latino et al (85). This score offers a standardized method of categorizing disease severity, therefore assessing burden of disease and guiding clinical trial design.

However, given the overall high rate of morbidity of alternative approaches, we recommend reserving them for patients in which liver transplantation is contraindicated. It must be noted that liver transplantation is the only curative option in intrahepatic HHT (86). It offers excellent post-transplantation survival rates (92% after a follow up of 109 months) and it significantly improves or completely reverses HOCF (74).

LTx should be considered early during the progression of symptomatic hepatic lesions in HHT patients, as it also improves quality of life post-transplantation (6). Moreover, because of the complex morbidity and high mortality of the disease, it is recommended to refer patients with serious HHT-associated complications to HHT excellence centres.

**HHT and MEN Type 1 Syndrome**

Our patient is the first reported case in whom hereditary haemorrhagic telangiectasia and
multiple endocrine neoplasia type 1 syndrome coexisted. The latter is a rare autosomal dominant inherited endocrine cancer syndrome which manifests with tumours of the parathyroid glands (95%), anterior pituitary (15-90%) and endocrine gastroenteropancreatic tract (30-80%) (87). The disease is caused by mutations in the MEN1 gene (OMIM 6137311q13.1), which encodes an aberrant variant of the normal protein named menin. Menin is a nuclear scaffold protein which regulates gene transcription by coordinating chromatin remodelling (88). It interferes with the Transforming Growth Factor beta (TGFβ) signalling pathways, playing an important role in TGFβ-induced growth inhibition (89). Therefore, the inactivation of menin disrupts TGFβ-mediated growth inhibition and transcription, which leads to tumour formation (90). It has been proven that the inactivation of menin in anterior pituitary cells blocks TGFβ and activin signalling, which in turn antagonizes their growth-inhibitory properties (90).

As we have shown, an aberrant TGFβ signalling pathway has been proven as the most important factor in the pathogenesis of HHT. Thus, judging by the clinical manifestations noted in our patient, it can be postulated that the co-existence of the HHT and MEN1 mutations has led to significant downstream TGFβ signalling pathway-associated manifestations.

Conclusion

The wide spectrum of clinical manifestations associated with HHT mandates a careful and exhaustive investigation of the patient before OLT, as any unnoticed AVM can precipitate potentially life-threatening complications after the procedure.

We have presented the case of HHT in a patient with a history of MEN type I (hitherto not reported). Taking in consideration that the arterial anastomosis in the setting of LTx for HHT is a very technically difficult procedure, an end-to-side anastomosis to the stump of the celiac trunk should be considered. Our case report shows that it is not only feasible, but it can represent the solution to the anastomotic calibre mismatch.

A potential pathogenetic link between the hereditary haemorrhagic telangiectasia and Multiple Endocrine Neoplasia type 1 syndrome via the TGFβ pathway, perhaps due to the effects of interactions between mutated activin and activin A receptor type II-like 1 genes, could be the subject of further studies.

Conflict of Interest

The authors declare no conflicts of interests.

Author’s Contributions

MII is principal author - designed and wrote the manuscript, performed literature research, examined clinical noting for case report; DT - reviewed the manuscript, provided intellectual input to and supervised the process of manuscript writing; CI, DIEN, SS - reviewed manuscript and provided input.

References

Orthotopic Liver Transplantation for Hereditary Hemorrhagic Telangiectasia and MEN Type I Syndrome – Case Report and Review of Literature


