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Casi clinici

Case reports

Extra-cerebral severe infections associated with haemorrhagic hereditary telangiectasia (Rendu-Osler-Weber Disease): five cases and a review of the literature

Complicanze infettive gravi extra-cerebrali in pazienti affetti da teleangectasia emorragica ereditaria (Malattia di Rendu-Osler-Weber). Cinque casi clinici e revisione della letteratura

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INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder that affects approximately 1 in 5000 people and that is characterised by genetically-determined abnormalities of the vascular structure [1]. Clinical diagnosis of HHT is based on the presence of multiple arteriovenous malformations (AVMs) and/or telangiectasia in characteristic locations and is sustained by international consensus diagnostic criteria, the Curaçao criteria, represented by the presence of epistaxis, mucocutaneous telangiectases (lips, oral cavity, finger tip and nose), visceral lesions (gastrointestinal telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs), and family history. Because of the age-related penetrance of this disorder, genetic testing is useful for the diagnosis in children and young adults whose relatives are affected [2]. Complications include haemothorax, cerebral stroke, subarachnoid haemorrhage and infections [3]. Infectious complications represent an important clinical aspect since people affected by HHT are predisposed to severe infections such as cerebral abscesses, in patients with pulmonary arteriovenous malformation (PAVMs), bacteraemia, septic arthritis, osteomyelitis, hepatic abscesses, skin infections and infective endocarditis (IE) [4].

Here we present five cases of severe bacterial extracerebral infections observed in patients affected by HHT, admitted to our Institute from January 2007 to June 2013. Patients' records were retrospectively reviewed in order to collect clinical data and information about previous HHT-related infections before admission to our hospital. As far as we know, a prosthetic joint infection has never been described in the literature as a complication of HHT. Furthermore, a review of the literature of the last five years was made using these terms: hemorrhagic, hereditary, telangiectasia, infectious, complications, infections.

CASE SERIES

Case 1

A 65-year-old Caucasian man complained of a two-month history of persistent fever with chills and asthenia. Prior to admission he was

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unsuccessfully treated with empiric antibiotic therapy prescribed by his general practitioner. The patient's medical history included HHT, diagnosed during his adolescence, blood hypertension, urinary lithiasis and biliary mud. On admission he was septic. Cutaneous telangiectases were present mainly on the lips, face and buccal mucosa. A systo-diastolic murmur (2/6) was present. Blood tests showed neutrophilic leukocytosis, moderate anaemia and abnormal values of C Reactive Protein (PCR) and sedimentation rate. Blood cultures were taken while the patient was feverish; transthoracic (TTE) and transesophageal (TEE) echocardiograms were negative for endocarditic vegetations. A colonoscopy showed no arteriovenous malformations at that level, nor any other portal of entry for microorganisms into the blood. The patient was stable and no empiric antibiotic therapy was started until blood cultures yielded *Streptococcus mutans*. Antimicrobial treatment with ceftriaxone and gentamicin was started. A transesophageal echocardiogram (TEE) failed to show endocarditis. In order to better define the source of bacteraemia the patient underwent a magnetic resonance of the whole column that showed D12-L1 spondylodiscitis (see Figure 1). Gentamicin was stopped and levofloxacin was started; the patient was successfully treated with i.v. ceftriaxone and oral levofloxacin in an outpatient regimen for eight weeks.

Figure 1 - D12-L1 Streptococcus mutans spondylodiscitis.

Case 2

A 69-year-old, Caucasian man was admitted to our division complaining of intermittent fever and chills for two weeks, unresponsive to antimicrobial therapy prescribed by his family physician. Diagnosis of HHT restricted to nasal mucosa had been made nine years previously and the patient referred familiarity for HHT (his father and a sister). The patient's medical history included ischemic heart disease, mitral insufficiency, abdominal aortic aneurism surgically treated and blood hypertension. On admission he was feverish and he had tachycardia. Skin and mucosa were pale. Lungs and abdomen examination was normal. Heart sounds were abnormal with a grade 3/6 systolic murmur best heard at the apex. Neutrophilic leukocytosis, moderate microcytic anaemia, elevated platelet count and abnormal values of PCR and sedimentation rate were present at the blood tests. Blood cultures on admission yielded a methicillin sensitive *S. aureus* (MSSA). A TEE was performed due to the high suspicion of infective endocarditis, and a sessile isoechogenic formation of cm 1.26x0.7 on the anteromedial leaflet of the mitralic valve was detected. An-

timicrobial treatment with oxacillin was started. The patient continued to be haemodynamically stable and his body temperature normalized. Cardiac surgeons did not advise surgical valve replacement. TEE was repeated and no vegetation was detected; the patient was finally discharged after four weeks of intravenous antibiotic treatment.

Case 3

A 63-year-old man was admitted to the emergency room of a tertiary care hospital complaining of continuous fever and a painful right knee. His medical history included a diagnosis of HHT (frequently complicated by prolonged epistaxis). In the ER an evacuative arthrocentesis was performed. No white blood cells count or microbiological cultures were performed. No infectious disease specialist consultation was requested nor was antimicrobial treatment started. The patient was discharged with an indication to take oral corticosteroid and non-steroidal anti-inflammatory drug treatment. Two weeks later, after a temporary amelioration, the patient's clinical conditions worsened and he was admitted to our hospital with a septic syndrome. The right knee was painful, swollen and warm.

The heart examination revealed abnormal sounds with a grade 2/6 systolic murmur, heard best at the apex. Blood tests revealed a high white cell count with an elevated percentage of neutrophils, mild anaemia and abnormal values of PCR and sedimentation rate. Blood cultures were taken and a diagnostic arthrocentesis was performed. Synovial fluid analysis revealed 45,000 WBC/µl, with 90% PMN and a methicillin-resistant *Staphylococcus aureus* grew a few days later from fluid culture. Antimicrobial therapy with trimethoprim sulfamethoxazole and rifampin was then started. The fever disappeared the day after. A TTE failed to show any endocarditis vegetations. The patient was discharged after a few days with the diagnosis of septic arthritis. He had progressive improvement of local symptoms with complete healing after three weeks. Antimicrobial therapy was interrupted at the end of the fourth week.

Case 4

A 73-year-old Caucasian woman was admitted to our hospital with a suspected prosthetic knee joint infection. She complained of a seven-day history of fever, chills and pain in the right knee, where a prosthetic joint had been implanted six months before. The patient's medical history included HHT with hepatic AVM, diabetes, hypothyroidism and a previous MSSA spondylodiscitis. Her clinical conditions were good except for warmth, effusion and local pain complained at the implant site. Blood tests showed neutrophilic leukocytosis, and elevated fasting glucose. No implant migration or periprosthetic osteolysis were present at the X-ray. A MSSA grew both from the cultural exam of synovial fluid removed by arthrocentesis and from the blood samples taken on admission. TTE was negative. Because of the acute onset symptoms, the stability of the prosthesis, the good condition of soft tissues and both rifampin and methicillin sensitivity of the SA isolated, the knee prosthesis was retained and antibiotic therapy with oxacillin i.v. and rifampin by oral administration was performed for 14 days. The patient was then transferred to the orthopaedic unit and a surgical debridement intervention was performed. Antibiotic oral therapy was subsequently prescribed for a period of six months.

Case 5

A 53-year-old Caucasian man complaining of fever and severe cervical pain was admitted to our hospital. His medical history included HIV infection, diabetes mellitus and HHT, complicated by prolonged epistaxis episodes in the past. He was on antiretroviral treatment with a good viro-immunological control of his HIV infection. On admission the patient was feverish and tachycardic. He had tachypnea and oxygen saturation was 93%.

Heart sounds, lungs and abdomen examination were normal. He had an elevated neutrophilic count and abnormal values of PCR and sedimentation rate. An empirical antibiotic therapy with piperacillin/tazobactam and vancomycin was started after blood cultures were performed. Red blood cell transfusions were administered. Since all blood cultures yielded MSSA, i.v. therapy with oxacillin was started and empirical treatment stopped. TTE excluded endocarditic vegetations. TEE was interrupted early because of profuse epistaxis starting at the beginning of the procedure. The magnetic resonance of the whole column showed structural alteration of cervical vertebrae without signs of spondylodiscitis. His clinical condition progressively improved and patient was discharged after 14 days of antimicrobial treatment.

DISCUSSION

According to data published prior to 2007, extracerebral infectious complications in those affected by HHT comprise 67% of all severe infections, and their incidence is high, being around 9% in the largest published cohort [4]. HHT patients affected by these infectious complications typically experience a longer median duration of epistaxis than HHT patients with

Table 1 - Extra-cerebral infective complications from the review of the literature of the last five years. HHT: Haemorrhagic Hereditary Telangiectasia.

Author/ Year	*N pts.*	*Clinical manifestation*	*Isolation sample*	*Microorganism*	*Treatment*	*Outcome*	*Previous HHT-related*
Dégot, 2012	1	Empyema	Pleural fluid	*Prevotella* sp. *Peptostreptococcus*	Surgical drainage and antimicrobial therapy	Successful outcome	Brain abscess
Bui, 2010	1	Liver abscess	Abscess fluid drainage	*Streptococcus anginosus*	Surgical drainage and antimicrobial therapy (cefotaxime, metronidazole, amoxicillin)	Successful outcome	Septic arthritis
Bally, 2011	1	Mitral valve endocarditis	Blood	Methicillin sensitive *Staphylococcus aureus*	Surgical replacement of the valve and antimicrobial therapy with oxacillin and gentamycin	Non infection related death	Empyema Abscess of leg soft tissues
Cottin, 2007	11	Abscess soft tissues (arm, calf, hip) (4) Tuberculosis (4) Septic hip arthritis (1) Axillary lymphadenitis (1) Liver abscess (1) Empyema (1) Acute bacterial meningitis (1) Aortic valve endocarditis (1) Acute pyelonephritis (1) Acute peritoneal infection (1) Acute brucellosis (1)	*Pasteurella multocida* (axillary lymphadenitis)				
Castiglioni, 2012	1	Perivalvular abscess of prosthetic aortic valve	None	Not identified	Surgical replacement of the valve and antimicrobial therapy	Successful outcome	None

cerebral abscesses or without infection. A longer median duration of epistaxis is a probable risk factor for such kinds of infections, since a prolonged presence of cotton packing for haemostasis causes a traumatism of the nasal mucosa and may favour nasal proliferation of *S. aureus*, the main pathogen isolated [4].

Review of the data published in the last five years concerning extracerebral complications in HHT patients has revealed 15 cases of extracerebral infections. They included soft tissue abscesses [n=4], tuberculosis [n=4], pleural empyema [n=2], liver abscesses [n=2], infective endocarditis [n=2], perivalvular abscess of prosthetic aortic valve [n=1], acute pyelonephritis [n=1], acute peritoneal infection [n=1], acute bacterial meningitis [n=1], septic hip arthritis [n=1], axillary lymphadenitis [n=1], and acute brucellosis [n=1], (Table 1) (3, 5-8). Microbiological data were often incomplete.

Extracerebral infections cases recovered in our Institute include: spondylodiscitis (n=1), native mitralic valve IE [n=1], bloodstream infection [n=2], septic arthritis [n=1] and prosthetic knee joint infection [n=1]. A prosthetic joint infection has never been described in people affected by HHT (Table 2). At the time of admission to our hospital most of our patients affected by SA infection had already experienced severe SA extracerebral infection, such as spondylodiscitis and repeated bacteraemia (Table 2). Extracerebral infectious cases described in the literature were also often recurrent.

Microbiological data of our case series and the literature review confirm that the source of infection in patients affected by HHT is usually endogenous (Tables 1 and 2). Indeed, we assume that in our cases of SA infection the entry route of the pathogen was probably the nasal mucosa, whilst the entry route of *S. mutans* causing spondylodiscitis could be the oral cavity or the gastrointestinal tract.

Table 2 - Extra-cerebral infective complications in people affected by HHT recovered in INMI "L. Spallanzani" from January 2007 to June 2013. HHT: Haemorrhagic Hereditary Telangiectasia Bid: twice a day, po: per os, qd: once a day, q4h: every 4 hours.

Case	*Underlying conditions/ Age*	*Type of infection*	*Microorganism*	*Isolation sample*	*Treatment*	*Outcome*	*Previous HHT related infections*
1	Hypertension/65	Spondylodiscitis	*Streptococcus mutans*	Blood	Ceftriaxone 2 g i.v. qd for 8 weeks, Levofloxacin 500 mg po bid for 8 weeks	Cure	None
2	Ischemic heart disease, Mitral insufficiency, Hypertension/69	Mitral valve endocarditis	MSSA	Blood	Oxacillin 2 g i.v. q4h for 4 weeks	Cure	Two episodes of MSSA bloodstream infection
3	Abdominal aortic aneurysm, Mitral insufficiency, Hypertension/63	Septic arthritis	MRSA	Synovial fluid	Trimethoprim sulfamethoxazole 160/800 mg po bid for 4 weeks, Rifampin 600 mg po qd for 4 weeks	Cure	Mitralic valve endocarditis
4	Diabetes mellitus, Hypothyroidism/73	Knee prosthetic joint infection	MSSA	Blood, Synovial fluid	Surgical Debridement + Oxacillin 2 g i.v. q4h for 4 weeks, Rifampin 600 mg po qd for 4 weeks	Lost at follow up	MSSA Spondylodiscitis
5	HIV infection, diabetes mellitus/53	Bloodstream infection	MSSA	Blood	Oxacillin 2 g i.v. q4h for 2 weeks	Cure	None

Extracerebral infection cases occur independently of the extent of HHT disease. By contrast, cerebral infectious complications are typical of HHT patients with PAVMs [4, 9]. Moreover, the extent of HHT disease usually influences the timing of such infectious complications; this is confirmed by our case series. Indeed, at the time of their first infectious complication our patients were older than people affected by PAVMs (Table 2). Few mortality data specific to infectious complications of HHT patients are found in the literature (Table 1); most of our cases had a successful clinical outcome (Table 2).

HHT patients should be considered at major risk of recurrent cerebral and severe extracerebral infectious complications, mostly due to endogenous microbiological flora (Table 1). Indeed, in order to prevent brain abscesses in people affected by HHT with PAVMs undergoing interventional dental procedures, antibiotic prophylaxis has already been recommended by the British Society for Antimicrobial Chemotherapy and Dental Formulary Sub-Committee [10].

The data from our study, albeit scant, may confirm that HHT patients are predisposed to severe extracerebral infectious complications. We observed a trend in recurrence in our cases and in those of the literature. Recurrent infections in our HHT patients were mostly related to SA, a typical colonizer of nasal mucosa.

A limit of our study is that SA nasal colonization of these patients was not assessed on admission or during subsequent follow-up after discharge. Colonization by SA has been recognized as a risk factor for nosocomial infections, and prophylactic mupirocin decolonization, together with bathing with chlorhexidine gluconate soap, is suggested in SA nasal carriers undergoing cardiothoracic procedures [11]. Moreover, non-surgical patients, like those undergoing dialysis or those affected by recurrent SA skin and soft tissue infections, may benefit from decolonization. However, little is known about the usefulness of SA colonization screening or a decolonization approach in HHT patients [12].

CONCLUSION

The association between HHT and infectious diseases has already been clearly demonstrated. Despite the small sample size, our study showed that HHT patients with infectious complications exclusively localized in extracerebral sites are usually old, fragile patients, and affected by comorbidities, and that a clear trend in recurrence of SA infections exists both in our cases and in cases from literature. Current guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections suggest SA decolonization only in people affected by recurrent surgical site infections despite wound care and optimisation of hygiene measures [12]. Even though we are aware that prolonged or repeated use of mupirocin may increase the risk of resistance development, we promote further studies in order to assess possible benefits of SA nasal colonization screening and decolonization in HHT patients without PAVMs with a history of SA recurrent extracerebral infections.

Keywords: haemorrhagic, hereditary, telangiectasia, infectious, complications.

SUMMARY

Hereditary haemorrhagic telangiectasia (HHT) is one of the most common autosomal dominant disorders and is characterized by genetically determined abnormalities of vascular structure. People affected by HHT are predisposed to severe infections such as cerebral abscesses, typical of patients with pulmonary arteriovenous malformations, and extra-cerebral infections such as bacteraemia, septic arthritis, osteomyelitis, hepatic abscesses, skin infections and infective endocarditis. We present a retrospective series of severe bacterial extra-cerebral infections in five patients affected by HHT, admitted to our Institute from January 2007 to June 2013. We also reviewed the literature of the last five years concerning infectious complications in people affected by HHT. Our study shows that HHT patients with infectious complications exclusively localized in extra-cerebral sites are usually fragile, old and affected by comorbidities. Moreover, we recognized a trend of *Staphylococcus aureus* (SA) severe infection recurrence in such patients, both in our series and in the literature. In our opinion these results suggest the need to evaluate the possible benefits of SA nasal colonization screening and decolonization in such patients.

RIASSUNTO

La teleangectasia emorragica ereditaria (EET) è una delle malattia autosomiche dominanti più comuni ed è caratterizzata da malformazioni arterovenose localizzate in vari distretti corporei.
I soggetti affetti da tale patologia sono predisposti a infezioni gravi come gli ascessi cerebrali, tipici dei portatori di malformazioni arterovenose polmonari, ed infezioni extra-cerebrali come batteriemie, artriti settiche, osteomieliti, ascessi epatici, infezioni di cute e tessuti molli, endocarditi infettive. Riportiamo in questo lavoro una serie retrospettiva di cinque casi di infezioni batteriche gravi localizzate in sedi extra-cerebrali in pazienti affetti da EET ricoverati nel nostro Istituto dal gennaio 2007 al giugno 2013, e una revisione della letteratura riguardante le complicanze infettive in soggetti affetti da EET pubblicata negli ultimi cinque anni. Sia nella nostra serie di casi che in letteratura i soggetti affetti da EET e complicanze infettive in siti extra-cerebrali sono tipicamente anziani con comorbilità; inoltre, abbiamo riscontrato una tendenza alla recidiva delle infezioni gravi determinate da Staphylococcus aureus *(SA). A nostro parere, questi risultati sottolineano la necessità di studi che valutino il possibile beneficio, in questa tipologia di pazienti, dello* screening *della colonizzazione nasale da parte di SA e della eventuale decolonizzazione.*

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