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Life-threatening thrombotic thrombocytopenic purpura associated with dental foci

Report of two cases

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Abstract

Background: Thrombotic thrombocytopenic purpura (TTP) is a rare haematological disease of unknown aetiology. This thrombotic microangiopathy is characterized by microvascular lesions with platelet aggregation. It is found in adults and can be associated with pregnancy, cancer, autoimmune diseases, bone marrow transplantation, drugs and bacterial as well as viral infections. The therapy requires a multi-disciplinary team approach involving dentistry. Even if TTP is immediately treated in an adequate manner, it still shows a mortality of up to 20%.

Aim: To define a specific treatment concept for periodontal disease and decayed teeth in patients suffering from TTP based on the experiences gained from two cases.

Conclusion: The two patient cases revealed a possible association of TTP with dental foci. Because of the severity and mortality of this disease, both prognosis evaluation and treatment standards of periodontologically compromised or decayed teeth have to be strictly followed in patients suffering from TTP. In order to avoid recurrence of TTP, it seems important to remove radically teeth of questionable prognosis.

Key words: dental foci; periodontal disease; systemic disease; thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multi-system disease characterized by the classic pentad of thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), neurological symptoms, progressive renal failure and fever.

The incidence of TTP is estimated to be 3–7 cases per year per 1 million persons (Bell et al. 1991, Moake 1994). The reported mortality rate has dramatically decreased during the past two decades. However, still up to 20% of the patients affected by this disease die despite adequate treatment (Quasim & Partridge 2001). The clinical presentation may vary considerably as the classic pentad is seen only in less than half of the patients. A prodromal period resembling a viral, flue-like syndrome is common. Thrombocytopenia can lead to purpura, ecchymosis or spontaneous bleeding. Subsequently, haematuria and renal failure occur. Neurological symptoms appear transiently and range from headache and confusion to seizures, hemiparesis and coma (Quasim & Partridge 2001).

The aetiology and pathogenesis of TTP are still not fully understood. Currently, it is assumed that an endothelial damage triggers processes leading to microvascular lesions with platelet fibrin microthrombi occluding arterioles and capillaries. Recent reports have shown that a deficiency regarding a specific plasma protease (ADAMTS13) being responsible for cleaving of the von Willebrand factor plays a crucial role in microthrombi formation (Furlan et al. 1998, Tsai & Lian 1998, Remuzzi et al. 2002). The latter hinders microcirculation and causes organ dysfunction like renal failure or hemiparesis by cerebral ischaemia.

The majority of TTP cases occur without a known precipitating factor. They are referred to as primary or idiopathic TTP. Secondary TTP shows an association with connective tissue disease, pregnancy, cancer and certain drugs like immunosuppressants. Moreover, viral and bacterial infections have been identified to be relevant aetiological factors (Neild 1994, Creager et al. 1998, Lara et al. 1999). A PUBMED query of the literature was performed to identify publications reporting an explicit association of TTP and dental infection (http://www.pubmed.de, date: 10–10–2003, keywords: TTP+foci/dental infection/oral infection/periodontal). The recherché yielded no results.

Actually, none of the reports dealing with TTP evaluates the role of dental foci in the occurrence and recurrence of the disease. Nevertheless, the detrimental effect of chronic dental infections on general health is well known. These are considered to deteriorate the condition of medically compromised patients (Golder & Drinnan 1993, Meurman 1997). It has been shown that periodontal disease is a risk factor for atherosclerosis and other chronic diseases (Seymour & Steele 1998, Garcia et al. 2001). As chronic diseases reveal a slow progression over time, dental treatment is focussed on preventive care to avoid dental infections. In contrast to chronic diseases, TTP exhibits a fulminant progression leading to death if it is diagnosed or treated on delay (Rock et al. 1991, Lau & Wun 1993).

Therefore, the aim of this presentation is to highlight the differences in concepts of treatment of dental foci between TTP and other systemic diseases.

Case Report 1

A 51-year-old non-smoking male presented at the Department of Medicine IV of the University of Erlangen-Nuremberg complaining of general malaise and fever over a period of 1 week. The patient reported two episodes of thrombocytopenia that had occurred 1 and 2 years ago. There was no history of other general diseases.

On initial examination, the patient was alert, oriented and did not show any signs of bleeding. Intraoral examination showed multiple mobile and decayed teeth. Laboratory examinations revealed a platelet count of 10,000/μl (reference range 140,000–400,000/μl) and a haemoglobin value of 9.1 g/dl (reference range 13.6–17.2 g/dl). Fragmented red blood cells (schistocytes) were observed in the peripheral blood smear. These cells were pathognomonic for MAHA. Based on the history of thrombocytopenia, the presence of fever and the laboratory studies showing MAHA the clinical diagnosis of TTP was established. The patient was transferred to the intensive care unit (ICU) where a therapeutic plasma exchange was carried out immediately with 2500 ml of fresh frozen plasma (FFP). Platelet counts returned to normal values after three additional plasma exchanges in the following days.

The patient showed no history of bone marrow transplantation or intake of drugs like immunosuppressants causing TTP. Different examinations were carried out to detect other factors that have been reported to be associated with TTP. For detection of infectious foci and cancerous lesions, a thorough physical examination was carried out including neurological and urological status. Moreover, an ultrasound examination of the abdomen and a computed tomography of the chest were performed. As no factors associated with TTP could be detected, the patient was scheduled for a dental examination by the Department of Oral and Maxillofacial Surgery of the University of Erlangen-Nuremberg. Unfortunately, he refused any further examination and treatment. The patient was discharged from the hospital after a total of six plasma exchanges (platelet count 285,000/μl) on day 8. At that time, all symptoms of TTP had disappeared.

Ten days after discharge, the patient again complained about increasing headache, nausea and arthralgies. On re-admission, the patient was disorientated and showed a focal neurological deficit. Laboratory studies revealed a platelet count of 4000/μl, as well as schistocytes in the peripheral blood smear. The patient was diagnosed with a relapse of TTP and was transferred to the ICU, where he received plasma exchange therapy for 10 days. At that time, the patient was referred to the Department of Oral and Maxillofacial Surgery of the University of Erlangen-Nuremberg. Intraoral examination revealed poor oral hygiene, characterized by massive plaque deposits along the cervical margins of the dentition. In both the mandible and maxilla, the gingiva displayed redness, swelling and bleeding on gentle probing as well as increased probing depth and attachment loss. Supragingival calculus was present on the lingual surfaces of the lower incisors. An increased mobility of grade II according to Miller's classification was observed in the lower central and lateral incisors and the lower right canine. Carious lesions were found in 14 of the remaining 20 teeth. A Water's view and a panoramic radiograph were assessed. The latter revealed an advanced alveolar bone loss in both jaws.

Oral surgical treatment was performed under local anaesthesia using 5 ml of local anaesthetic (articain 0.4 mg/ml, epinephrine 0.006 mg/ml; Ultracain-DS 1:200,000, Aventis, Bad Soden, Germany). A single-shot intravenous antibiotic prophylaxis with 10 million IU penicillin G (Penicillin G ''Grünenthal'' 10 Mega, Grünenthal, Aachen, Germany) was administered perioperatively. At that time, platelet counts had normalized (285,000/μl). Surgical treatment involved removal of the five teeth showing mobility of grade II as well as scaling and root planing at a single appointment. Excavation and restoration of carious lesions were performed at a second appointment. After the patient was discharged from the hospital, he received further restorative and prosthetic therapy and was restored with a removable partial denture. During a follow-up of 14 months, there was no recurrence of TTP.

Case Report 2

A 40-year-old non-smoking female was referred to the Department of Medicine IV of the University of Erlangen-Nuremberg after a gynaecological examination because of massive vaginal bleeding. The patient reported a feeling of lethargy and malaise for several days before the bleeding suddenly occurred. The previous medical history was uneventful.

On admission, the patient was disorientated and developed cerebral palsy. Within a few hours, she became comatose, and had to be put on a respirator. Physical examination revealed petechiae and ecchymoses on the tibial regions as well as multiple carious lesions, mobile teeth and desolate oral hygiene. Laboratory examinations showed a platelet count of 4000/μl (reference range 140,000–400,000/μl), a haemoglobin of 7.8 g/dl (reference range 12.0–15.0 g/dl) and schistocytes in the peripheral blood smear. TTP was diagnosed, based on clinical symptoms and the results of laboratory examination. The patient was transferred to the ICU where a plasma exchange was carried out with 2500 ml of FFP. Platelet counts gradually returned to normal values, whereas the neurological deficit resolved very slowly. Plasma exchange therapy continued for 18 days. In order to detect infectious causes of secondary TTP, a thorough physical examination was carried out including neurological and gynaecological examination. Conventional radiological studies, ultrasound examination of the abdomen,

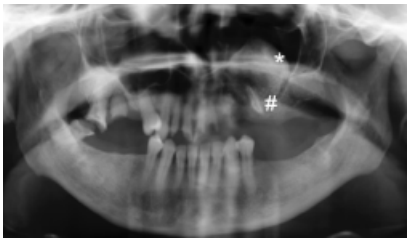

Fig. 1. Preoperative panoramic radiograph showing a root fragment (#) in the upper left alveolar process and an opaque mass in the left maxillary sinus (*).

computed tomography scans of the chest and magnetic resonance imaging scans of the neurocranium were performed, but yielded no pathological results. Subsequently, the patient was referred to the Department of Oral and Maxillofacial Surgery of Erlangen-Nuremberg University. On examination, the gingiva was swollen and showed bleeding on gentle probing. Decayed root fragments were found in the position of the first and second upper right molars, the left upper lateral and central incisors and the left upper canine. Nine out of 18 teeth showed carious lesions. A panoramic radiograph revealed advanced resorption of the alveolar crest. Panoramic radiograph and Water's view showed an opaque mass of 2 cm diameter on the floor of the left maxillary sinus (Fig. 1). A computed tomography was carried out for further evaluation of this process.

At the time the oral surgical treatment was performed, the patient was in good physical condition and platelet counts as well as other laboratory findings had normalized. A single-shot intravenous antibiotic prophylaxis with 10 million IU penicillin G (Penicillin G) was administered perioperatively. Oral surgical treatment comprised removal of the root fragments and the partially erupted right lower third molar under local anaesthesia using 7 ml of local anaesthetic (articain 0.4 mg/ml, epinephrine 0.006 mg/ml; Ultracain-DS 1:200,000, Aventis). Revision of the left maxillary sinus was carried out by an approach through the lateral antral wall (Fig. 2). A root fragment that had been dislocated into the sinus during an extraction performed previously alio loco was removed together with polypous antral mucosa (Figs 3 and 4). Histological examination revealed a chronic inflammation of the antral mucosa without signs of malignancy.

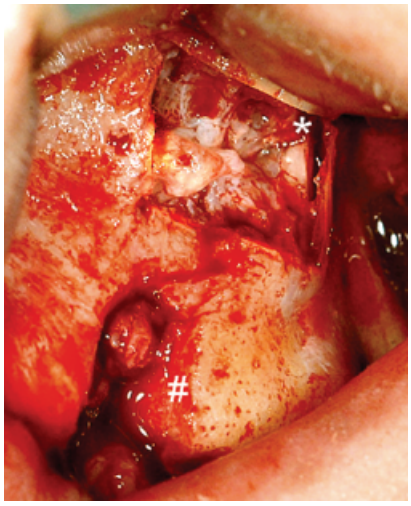

Fig. 2. Clinical situation after the removal of the left lateral antral wall showing granulation tissue within the left maxillary sinus (*) and the root fragment in the alveolar process (#).

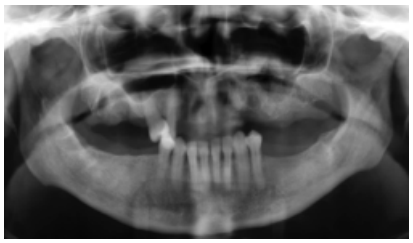

Fig. 3. Postoperative panoramic radiograph after removal of decayed teeth and revision of the left maxillary sinus.

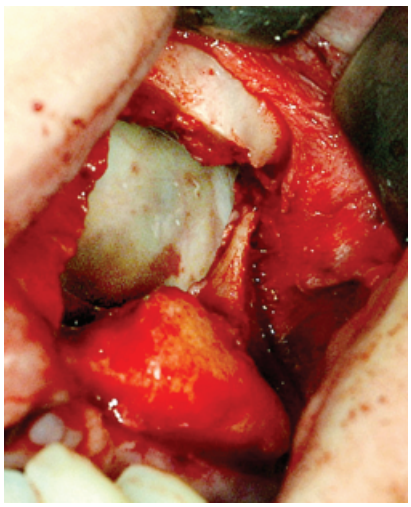

Fig. 4. Clinical situation after removal of the root fragment and the granulation tissue.

On day 29, the patient was discharged from the hospital (platelet count 200,000/μl). During a subsequent follow-up of 6 months, TTP did not re-occur.

Discussion

The occurrence of TTP is a haematological emergency situation. It is a multisystem disease that can cause rapid deterioration of the patient's neurological, renal and haematological status. TTP is an uncommon disease with high mortality if untreated or misdiagnosed. Rapid diagnosis and aggressive treatment by therapeutic plasma exchange are necessary to reduce the risk of fatal outcome (Bell et al. 1991, Lara et al. 1999). However, 20–40% of surviving patients have relapses. These can occur as early as a few months after recovery, but also after an interval of many years (Real et al. 1998).

Initially, TTP is sometimes difficult to diagnose because the patient's symptoms can be non-specific. Often, the patient does not exhibit the complete characteristic pentad of thrombocytopenia, MAHA, neurological symptoms, progressive renal failure and fever. Other haematological diseases may have some of the same symptoms. However, in the presence of MAHA (schistocytes, elevated lactate dehydrogenase, and indirect hyperbilirubinaemia) as well as thrombocytopenia in the absence of other obvious causes (disseminated intravascular coagulation (DIC), malignant hypertension), TTP has to be considered a potential diagnosis and total plasma exchange has to be started immediately.

In the two present cases, none of the factors previously associated with secondary TTP like connective tissue disease, pregnancy, cancer and the use of certain drugs could be detected. Yet, both patients showed a large number of decayed or periodontologically compromised teeth with extensive probing depths and tooth mobility. The desolate dental status as a cause of chronic infection remained the potentially aetiological factor. Further studies are needed to evaluate the role of dental foci in the pathogenesis of TTP.

Generally, the strategy for treatment of dental foci depends on the patient's general health and the severity of the underlying systemic disease. Conflicting opinions can be found in the literature regarding the intensity of the treatment of dentogenic foci. In many chronic systemic diseases, more conservative therapy concepts are adopted, while patients undergoing radiotherapy still seem to require a more radical approach (Meyer et al. 1999, Thorn et al. 2000,

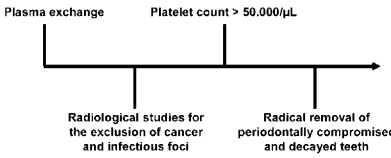

Fig. 5. Course of treatment concept.

Groetz et al. 2001, Lund et al. 2002). The same seems to be true for TTP, because the oral surgical treatment for elimination of dental infection sources as potential aetiological factors of TTP has to be taken into consideration facing the mortality rate of this particular disease. The possible significance of evaluation and complete removal of dental foci in TTP patients is shown in Case Report 1. The patient had suffered three episodes of TTP within 3 consecutive years. Even though platelet counts had recovered completely during the current episode, the disease reappeared within a few days after dismissal, while the patient refused to receive a radical extraction therapy of the compromised teeth. Early recurrence of TTP has also been described previously for other remaining infectious foci that had not been eradicated completely during the course of the disease (Creager et al. 1998, Niv et al. 2000, Kanj et al. 2003). Therefore, a conservative approach to dental rehabilitation in TTP may not be appropriate and severely compromised teeth should not be maintained.

Dental treatment of the affected patient should be started a soon as possible, as the patient's prognosis is fundamentally dependent on early diagnosis and treatment without delay (Quasim & Partridge 2001). However, a minimal platelet count of 50,000/μl should be re-established to prevent the occurrence of haemorrhage after extraction therapy (British Committee for Standards in Hematology 2003) (Fig. 5).

The potential dental sources of infection are well known (Siminoski 1993, Wang et al. 1996, Seymour et al. 2003). They comprise periapical abscesses, periodontal abscesses, deep vertical periodontal bone pockets exceeding 6 mm in probing depth, furcation lesions of multi-rooted teeth, deep carious lesions, pericoronitis of erupted or retained teeth such as third molars, cysts and mucosal ulcers (Meurman 1997, Gregg et al. 2002).

Prior to dental treatment, a radiological examination should be carried out involving single-tooth radiographs, panoramic radiographs and Water's views to exclude pathology of the maxillary sinuses. In cases of doubt, computed tomography has to be considered for further analysis of accompanying infectious diseases of the head and neck. Often, this examination can be combined with computed tomography of other regions also carried out for detection of cancerous lesions or infectious foci. In Case Report 2, a root fragment was found having been dislocated previously into the maxillary sinus during an extraction alio loco. It caused an infection of the maxillary sinus, which had to be treated by an approach through the lateral antral wall.

During the removal of teeth, a bacteraemia is likely to occur in a high percentage of cases, which may harm the patient. Therefore, administration of antibiotics and extraction of only one tooth at each appointment have been recommended (Okabe et al. 1995). However, in an urgent situation like in the two patient cases, 10 million IU penicillin G (Penicillin G) can be given intravenously as a single-shot prophylaxis, while we recommend the extraction therapy to be performed at a single appointment. As no relapse of the disease occurred, this treatment strategy seems to be appropriate.

Conclusion

As the mortality of TTP accounts for 20% of the cases and a high risk of recurrence arises from inadequate treatment of infectious foci, it seems that teeth with questionable prognosis should be removed radically using antibiotic prophylaxis after a minimal platelet count of 50,000/μl has been reached.

This hypothesis, however, has to be proven by follow-up of a larger series of cases.

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