DISSEMINATED CEREBRAL THROMBOTIC MICROANGIOPATHY IN A PATIENT WITH ADULT’S STILL DISEASE

Renan B. Domingues1, Ana Maria Casati da Gama2, Eliana B. Caser2, Carlos Musso3, Maria Carmen S. Santos3

ABSTRACT - Objective: The aim of this report is to describe a fatal disseminated thrombotic microangiopathy with renal, pancreatic, and cerebral involvement in a patient with recently diagnosed adult’s Still disease (ASD). Case report: A previously healthy 15 year old girl was admitted to our hospital. According to the clinical and laboratory data the diagnosis of adult’s Still Disease was established. The treatment was begun and a few days after an initial improvement a sudden neurologic deterioration with coma and seizures has occurred. Hours later the patient died. Clinical, laboratorial, and pathologic data will be presented. Conclusion: To our knowledge this is the second description of a fatal disseminated cerebral thrombotic microangiopathy in a patient with adult’s Still disease, but with a much more fulminating evolution than previously reported. Some etiopathogenic mechanisms could be shared in these two disorders explaining this coexistence.

KEY WORDS: adult’s Still disease, cerebral thrombotic microangiopathy, thrombotic thrombocytopenic purpura.

Microangiopatia trombótica cerebral em um paciente com doença de Still do adulto

RESUMO - Objetivo: O objetivo deste estudo é relatar um caso fatal de microangiopatia trombótica, com envolvimento dos rins, pâncreas e cérebro, concomitantemente a um quadro recém diagnosticado de doença de Still do adulto. Caso: Uma paciente de 15 anos, previamente saudável, foi admitida em nosso serviço. Os dados clínicos e laboratoriais levaram ao diagnóstico de doença de Still do adulto. Após alguns dias do início do tratamento e uma melhora inicial, houve súbita deterioração do nível de consciência e convulsões, tendo a paciente evoluido para o óbito horas após. Os dados clínicos, laboratoriais e anátomo patológicos serão apresentados. Conclusão: Trata-se do segundo caso fatal de microangiopatia trombótica fatal em paciente com doença de Still do adulto, mas com evolução neurológica muito mais rápida e fulminante que no caso anteriormente descrito. Mecanismos etiopatogenéticos comuns poderiam explicar a coexistência destas duas doenças.

PALAVRAS-CHAVE: doença de Still do adulto, púrpura trombocitogênica trombótica, microangiopatia trombótica.

Adult’s Still disease (ASD) has been recognized as a cause of fever, arthritis, evanescent maculopapular rash, myalgia, serositis, and leukocytosis. No specific serologic abnormalities or definitive etiology has been determined. The diagnosis of ASD is based on clinical findings as well as exclusion of other febrile polyarthritis1. Central nervous system manifestations have been described and include pyramidal tract signs, cranial nerve disorders, seizures, brainstem hemorrhage, and peripheral neuropathy. Some of these abnormalities are associated with drug toxicity, infections, or vasculitis2.

Here we report a patient with ASD who developed an acute neurological disease with intracranial hypertension associated with acute pancreatitis and acute renal failure. This fatal systemic disease was due to a disseminated thrombotic microangiopathy disease compatible with thrombotic thrombocytopenic purpura (TTP)/adult hemolytic uremic syndrome (HUS) (HUS/TTP syndrome).

CASE
A 15 year-old girl was admitted to the hospital with a 2-months history of intermittent high fever, migratory
polyarthritis involving her wrists, knees, and ankles, eva-
nescent macular skin rash, myalgias, and prostration. There
were not lymphoadenopathy and hepatoesplenomegaly. The
neurologic examination was initially normal. The white
blood cell (WBC) count was 28,500/mm3 (90% neutro-
phils), platelets 440,000/mm3, hemoglobin 9.4 gm/dl, reti-
culocyte count was 3.7%. Prothrombin activity (PA) was
72%, activated partial thromboplastin (APTT) time was 30
s. Blood urea was 18 mg/dl, creatinine 0.7 mg/dl; indirect
and direct bilirubin were 0.2 and 0.3 mg/dl, respectively;
serum glutamic oxalacetic transaminase (SGOT) 32 IU, se-
rum glutamic pyruvic transaminase (SGPT) 38 IU; amylase
30 U/l; urianalysis revealed 8-10 white cells per field and protein traces. Blood and urine cultures were negative.

Anti-streptolysis O titer was within normal values, antibo-
dies to nuclear antigens, complement levels, and VDRL
were negative. HIV antibodies, hepatitis B surface antigen,
and hepatitis C antibodies were negative. Chest radio-
graphy, eletrocardiogram, and transthoracic echocardi-
ogram were normal.

She was initially treated with aspirin (3g/day) and pred-
nisone (30 mg/day). Within 48 h there was a marked improve-
ment in arthritis and constitutional symptoms. Thirteen
days later the patient became suddenly confuse and agi-
tated. Few minutes later a tonic-clonic generalized seizure
was registered. She remained comatose after the seizure.

Acute renal failure (blood urea 174 mg/dl, creatinine 5.7
mg/dl) and pancreatitis (amylase 2831 U/l) were detected
at this time. The WBC count was 64,100/mm3, platelets
84,000/mm3. Prothrombin activity was 70%, activated par-
tial thromboplastin time was 35 s. Urinary albumina was
significantly increased (+++/4+). Therapy with methyl-
prednisolone 1000 mg/day was initiated. However, one
day later her neurologic examination showed Glasgow
coma scale 3, and bilateral paralytic midniasis.

Macroscopic findings at autopsy were acute fibrinous
pericarditis, signs of widespread renal cortical necrosis,
and edematous acute pancreatitis. The brain weighed
1150g. Diffuse edema and brainstem herniation were seen.
Microscopic findings were fibrinous pericarditis and epi-
carditis, sinusitis with mononuclear inflammatory infiltrate
with lymphocytes and plasma cells, renal thrombotic mi-
croangiopathy with thickening of capillary walls, deposits
of fibrin related materials in the capillary lumens, suben-
dothelium, mesangium, interlobular and afferent arteri-
oles, with aneurisimatic dilatation of some of those ves-
sels, thrombotic microangiopathy of the pancreas with fibrin
deposits in the arterioles, leading to coagulative necrosis
foci. Brain microscopic evaluation has disclosed fibrin rela-
ted material deposits in the arterioles, accompanied by
localized endothelial cell proliferation and detachment,
and widespread necrosis foci.

DISCUSSION
The diagnosis of adult’s Still disease in this case
was based on the age of onset of symptoms, clinical
picture, laboratorial data, and the exclusion of other
diseases. Although there were several signs usually
found in systemic lupus erythematosus, the possi-
bility of this diagnosis was remote since antinuclear
antibodies and serum complement were within nor-
mal values. The diagnosis of rheumatic fever was
ruled out since anti-streptolysin O and echocardi-
ogram were normal. This last finding as well as nega-
tive blood cultures excluded infective endocarditis. Three
hypothesis were listed to explain the sudden
neurological deterioriation and the systemic com-
lications: consumption coagulopathy, aspirin tox-
icity, and thrombotic microangiopathy.

Disseminated intravascular coagulation is a syndro-
me characterized by increased PA and APTT, de-
creased platelet count, and decreased levels of fibrino-
gen. Some cases of adult’s Still disease associated with
this coagulopathy have been described. In this case,
platelet count has decreased during the disease but fibrinogen level could not be assessed. However PA
and APTT remained within initial levels even after the
neurological deterioration. Since the coagulation tests
abnormalities characterize this entity it is unlike this
patient had disseminated intravascular coagulation.
Also, thrombi in disseminated intravascular coagula-
tion are usually predominant in the capillaries and ane-
urisimatic dilatation of arterioles are not usually seen.

Aspirin toxicity has been described in association
with adult’s Still disease. This condition is charac-
terized by severe hepatotoxicity and disseminated in-
travascular coagulation. Although aspirin was intro-
duced this association was ruled out since the patient
had normal SGOT and SGPT levels and there were
not hepatic disease at autopsy.

Thrombotic microangiopathies include throm-
botic thrombocytopenic purpura (TTP) and Hemolytic
Uremic Syndrome (HUS). These diseases show con-
siderable overlap. TTP is classically a pentad of throm-
boctopenia, microangiopathic hemolytic anemia,
neurologic abnormalities, renal dysfunction, and fe-
ver. Hemolytic-uremic syndrome (HUS) is part of the
spectrum of TTP-related disorders, defined by a triad
of thrombocytopenia, microangiopathic hemolytic
anemia, and renal dysfunction. Idiopathic TTP and
sporadic HUS, but not diarrhea, malignancy, or most
drug-associated forms of TTP/HUS, are closely related
in terms of response to therapeutic plasmapheresis
and distribution of pathologic lesions, and they are
now termed HUS/TTP syndrome. Three cases of TTP
in patients adult’s Still disease have been described.
The first reported case with this rare association was
a 45 year-old woman with a chronic adult Still’s di-
sease that has developed in that last thirteen years.
After this time she has developed purpura, renal dysfunction, and altered level of consciousness. The post-mortem examination revealed extensive thrombotic microangiopathy involving the lungs, heart, pancreas, thyroid, adrenal, lymphonodes, and bone marrow. Two other cases without fatal outcome were reported. The first was a thirty-three-year-old woman that presented clinical findings compatible with adult’s Still disease and eight months later developed hemolytic anemia, severe thrombocytopenia, neurologic symptoms, and mild renal dysfunction. She was treated with exchange plasmapheresis, fresh frozen plasma infusions, methylprednisolone 250 mg/day, and aspirin. Three days later the patient improved. The last case was a 28-year-old woman that developed adult’s Still disease and five months later was admitted with microangiopathic hemolytic anemia, thrombocytopenia, polymorphonuclear leukocytosis, neurological findings, and mild renal failure. Treatment with fresh frozen plasma and high dose steroids was initiated and the patient was discharged home after 60 days.

All the cases with adult’s Still disease and thrombotic microangiopathy were female patients. Our patient was younger than the other cases. In the other patients TTP has developed later in the course of adult’s Still disease but our patient developed thrombocytopenia soon after the beginning of arthritis and fever. Indeed our patient has had a sudden evolution to coma with signs of brain herniation that was not observed in previous cases. To our knowledge this is the second description of a fatal disseminated thrombotic microangiopathy within cerebral vessels in a patient with ASD. Our patient was treated with aspirin and usual dose of steroids from the beginning of the hospital admission. When the clinical deterioration was seen high dose steroids associated with support measures like hyperventilation and dialysis were tried but they did not prevent death.

The thrombotic microangiopathies are characterized pathologically by the development of platelet microthrombi that occlude small arterioles and capillaries and clinically by microangiopathic hemolytic anemia and thrombocytopenia. Endothelial dysfunction plays a prominent role in the pathogenesis of HUS and TTP. Endotelial injury determines microangiopathy by endothelial denudation. Endotelial injury and activation triggers can be bacterial endotoxins, cytokines, viruses, drugs, and antiendothelial antibodies. Microangiopathy follows endothelial injury due to exposition of subendothelial thrombogenic substances, reduced production of prostaglandin I2 and nitric oxide enhancing platelet aggregation and causing vasoconstriction, increased adhesivity of activated endothelial cells to leukocytes, elaboration of abnormal multimers of Van Willebrand factor. More recently, plasma from patients with thrombotic microangiopathy has been reported to induce apoptosis in endothelial cells; the plasma factors responsible for these changes remain to be identified. Adult’s Still disease etiology remains unknown. Several isolated reports have suggested a viral trigger in the pathogenesis of ASD. Other possibility is that ASD is a non-necrotizing immune complex vasculitis. Some studies have found genetic predisposition and associations with HLA-DR2, DR-4, DR-7. The coexistence of these two disorders could be just a coincidence or they could share similar pathogenetic mechanisms. A viral trigger, antiendothelial antibodies, immune complex deposits, and cytokines production could theoretically be seen in and auto immune disease like ASD. One or several of these pathogenetic mechanisms could precipitate endothelial injury and activation that could determine the thrombotic microangiopathy. The association between thrombotic microangiopathy and other auto immune disorders like systemic lupus eritematosus, sclerderma, and Sjögren’s syndrome reinforces this possibility.

REFERENCES