Inflammatory myofibroblastic tumor of the mesentery associated with high fever and positive Widal test

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ABSTRACT

يترافق الورم العضلي الليفي الالتهابي في 15%–30 من الحالات بأعراض عامة كالحرارة المرتفعة المستمرة، نقص في الوزن، ارتفاع سرعة تسرب الكريات الحمراء، فقر الدم، ارتفاع عدد الصفيحات الدموية والكريات البيضاء. في هذا التقرير نستعرض حالة لطفل لبناني يبلغ من العمر 4 أعوام، حضر إلى المستشفى مع ارتفاع مستمر في درجة الحرارة، و نتيجة اختبار ويدال للتراص مفردة وموجبة (غيد مقصر). كانت نتيجة فحص الدم سالبة، وتم تشخيص حالتة بحمى التيفوئيد. بعد 30 يوماً من ظهور الحرارة اكتُشف صدفتاً وجود ورم عضلي ليفي التهابي. أجريت له عملية جراحية، بعدها اختفت الحرارة نهائياً وعادت سرعة التنقل إلى المستوى الطبيعي. رجحنا إمكانية حدوث ايجابية كاذبة لاختبار ويدال، لوجود ارتفاع متعدد النسائل في مصل الجلوبين المناعي، وهذا ما يحدث عادة في الورم العضلي الليفي الالتهابي. إضافتاً إلى ذلك، نعتقد أن الورم العضلي الليفي الالتهابي مقلد ومحاكي لحمى التيفوئيد مخبرياً وسريرياً. وعليه، يجب على الأطباء وخاصة أطباء الأطفال الذين يعملون في المناطق الموبوءة أن يعيروا الانتباه إلى هذه المحاكاة.

Inflammatory myofibroblastic tumor (IMT) is associated in 15-30% of cases with systemic symptomatology, such as prolonged fever, weight loss, elevated erythrocyte sedimentation rate (ESR), anemia, thrombocytosis, and leukocytosis. We report the case of a 4-year-old Lebanese boy who presented with high-grade fever of long duration, and a single (unpaired) positive Widal agglutination test. Blood culture was negative. A diagnosis of typhoid fever was made. An abdominal (mesenteric) IMT was incidentally discovered, 30 days after the fever had appeared. After surgery, the fever disappeared immediately, and the ESR returned to normal. We strongly favor the possibility of a false positive Widal test, due to polyclonal increase in serum immunoglobulins, which often occurs in IMT. We also think that IMT might be a mimicker of typhoid fever, both clinically and serologically. Physicians, especially pediatricians practicing in endemic areas, should probably be aware of this mimicry.

Saudi Med J 2008; Vol. 29 (12): 1819-1823

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Received 31st May 2008. Accepted 9th November 2008.

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Inflammatory myofibroblastic tumor (IMT) was first described in the lungs. Later, many extra pulmonary cases have been reported individually and as a large series. It has been described in almost every organ including the mesentery, abdominal viscera, urinary bladder, kidney, heart, central nervous system, peripheral nerve, breast, orbit, skin, soft tissue, larynx and bone.[1] Extrapulmonary forms occur more often in children and young adults, with a slight female predominance, the mesentery being the most common location.[2,3] More archaic and less used terms are: inflammatory pseudotumor, post-inflammatory tumor, plasma cell tumor, and plasma cell granuloma. Signs and symptoms are related to the site of the tumor (namely, hematuria, jaundice, hoarseness, intussusception, syncope).[1] In approximately 15-30% of cases, the patient may experience systemic abnormalities, such as prolonged fever of unknown origin, weight loss, growth failure, malaise, anemia, leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate (ESR), and polyclonal increase in serum immunoglobulins (polyclonal hypergammaglobulinemia).[2,4] The clinical and laboratory anomalies are known to regress within days, or few weeks after the resection of the tumor.[4,5] In this article, we report the case of a 4-year-old Lebanese boy with mesenteric IMT, whose initial clinical presentation and serology tests strongly mimicked those of typhoid fever (enteric fever). We think that physicians, especially pediatricians practicing in the endemic areas, should be aware of this mimicry so that a delay in diagnosis and

unnecessary antibiotic therapy are avoided, and the appropriate treatment (surgery) is provided as soon as possible.

Case Report. A 4-year-old boy presented to Saint George Hospital University Medical Center, Beirut, Lebanon in October 2003 for a right-sided abdominal mass. One month prior to admission, he started complaining of high-grade fever (39-40°C), and cough. An upper respiratory tract infection was suspected, and he was placed on amoxicillin-clavulanic acid for 10 days without improvement. The fever appeared at night, and resolved in the morning, along with night sweats. It was not relieved by antipyretics. Laboratory tests showed: hemoglobin: 8.9g/dl (14-18 g/dl), white blood cell (WBC): 9500/µL (4800-10800/µL), neutrophils: 45% (43-65%), lymphocytes: 38% (20.5-45.5%), ESR: 53 mm (5-10 mm), and C-reactive protein (CRP): 14.7 mg/dl (0-0.5mg/dl). Three weeks later, a Widal serology test was ordered, and was positive titer of agglutinin O (TO): 1/160, titer of agglutinin H (TH): 1/320 (TO<1/100; TH <1/100). Blood culture was negative. He was diagnosed with typhoid fever and placed on cefixime. On a follow-up visit 10 days later, an abdominal mass over the right flank was palpated. He was then admitted for further investigation.

Upon admission, he was pale, and had low grade fever (38.2°C). A mass was palpable over the right flank (6x6 cm, hard, fixed, and non-tender). No adenopathy or hepatosplenomegaly were noted. Complete blood count (CBC) revealed anemia (Hb=8.8 g/d [14-18 g/dl]), thrombocytosis (986,000/µL [130000 -400000/µL]), and leukocytosis (17500/µL [4800-10800/µL]). The percentage of neutrophils (55%), and lymphocytes (42%) were within normal limits. Serum chemistry and coagulation studies were all normal. Serology test for infectious mononucleosis was negative. A peripheral smear showed hypochromic anemia with poikilocytosis, and the presence of rare atypical lymphocytes. No blasts were seen. Bone marrow aspirate was normal.

Plain film of the abdomen was normal. Abdominal ultrasound revealed an 8x6x3.5 cm soft tissue mass in the right subhepatic space, anterior to the lower pole of the right kidney, and extending to the anterior abdominal wall. Computed tomography (CT) scan of the abdomen confirmed the presence of an enhancing soft tissue mass, extending from the subhepatic space to the right iliac fossa, anterior and inferior to the right kidney, displacing the right colon medially, and lying on the right psoas muscle (**Figure 1**). Intraoperatively, a large mass (8x5.5x4 cm) was found in the retro-cecal area (**Figure 2**). It was adherent to the vermiform appendix and the cecum. Pathology consultation (frozen section) revealed a "spindle cell neoplasm," and definitive diagnosis was deferred to permanent (routine) sections. The mass was resected "en bloc" with the vermiform appendix. After surgery, the fever subsided, and the ESR returned to normal. Feeding was resumed on day 3, and the patient was discharged on day 7. He is in good health since the operation. On the last follow up (March 2008), CBC and ESR were normal. Abdominal ultrasound was also unremarkable. No mass was present.

Pathology findings. A well-circumscribed solid gray white firm mass measuring 8x5.5x4 cm was received. The external aspect was smooth and glistening. It was adherent to the vermiform appendix, which appeared otherwise unremarkable. Histology confirmed the absence of involvement of the appendix, which was normal. The interface between the mass and the surrounding mesenteric adipose tissue was smooth and regular. Irregular infiltrating tongues of spindle cells and entrapped adipose tissue were absent. The

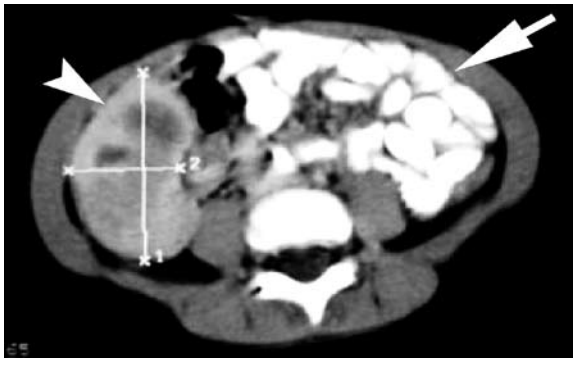

Figure 1 - Computed tomography of the abdomen after colonic and intra venous contrast showing an enhancing mass (8x6x3.5cm) (white arrowhead), anterior and inferior to the right kidney, lying over the right psoas. The white arrow points to the bowels filled with contrast material.

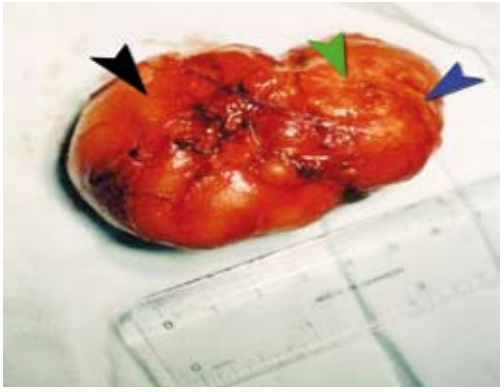

Figure 2 - Peroperative finding of a mass (black arrowhead), adherent to the cecum (green arrowhead) and to the vermiform appendix (blue arrowhead).

mass consisted of a proliferation of spindle shaped mesenchymal cells. Growth pattern was predominantly fascicular (**Figure 3**), with occasional small storiform areas. No myxoid matrix was present. Nuclei were oval to plump, displaying an open delicate vesicular chromatin, and small inconspicuous nucleolus. Nuclear pleomorphism was mild (**Figure 4**). Moderate to severe cytological atypia, ganglia like cells, and abnormal mitotic figures were absent. Background showed abundant intimately admixed plasma cells, lymphocytes, histiocytes, rare eosinophils, and neutrophils (**Figure 4**). Hemangiopericytoma like, vascular pattern, fat necrosis, lipoblasts, and broad fibrous bands of connective tissue, containing scattered atypical mononucleated and multinucleated giant cells were all absent.

No tumor necrosis was seen. Surgical resection margins were free of neoplasia. Castelman's disease like changes in the mesenteric lymph nodes were absent (3 lymph nodes). Ziehl-Neelsen and Fite stains revealed no acid-fast microorganisms. Immunohistochemistry showed only diffuse strong positive immunoreactivity of the neoplastic cells with anti vimentin and anti smooth muscle actin (SMA) antibodies, and weak diffuse immunoreactivity with anti muscle specific actin (MSA) antibody. The neoplastic cells showed absence of immunoreactivity with all of the following antibodies: anti-desmin, anti S-100, anti-CD117 (c-kit), anti-CD 34, and anti-CD21.

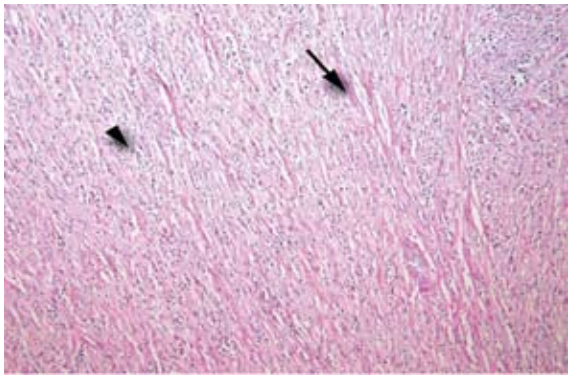

Figure 3 - Fascicular growth pattern. The arrow points to the delicate collagen bundles. Arrowhead points to the inflammatory and myofibroblastic cells in the background (Hematoxylin and Eosin 100x).

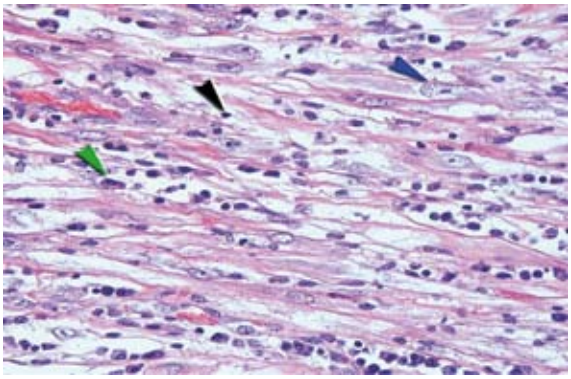

Figure 4 - Proliferation of spindle shaped cells (blue arrowhead) with plump to oval nuclei, absent to minimal pleomorphism, finely granular chromatin and inconspicuous nucleoli. Numerous plasma cells (green arrowhead) and lymphocytes (black arrowhead) are present in the background (Hematoxylin and Eosin 400x)

Discussion. In the current World Health Organization (WHO) classification, IMT is regarded as an intermediate, locally recurrent, rarely metastasizing neoplasm of myofibroblastic cells.[6] Cytogenetic and molecular biology studies have shown that 50-70% of cases harbor a clonal cytogenetic alteration, which involves the anaplastic lymphoma kinase (ALK) gene locus at 2p23.[6,7] Clinical diagnosis remains a challenge, as no clinical sign or symptom, nor is the laboratory finding specific for these tumors.

The diagnosis is histological, based on the identification of myofibroblastic proliferation with 3 main growth patterns, often found in combination:[1,2] (a) fasciitis-like with numerous polyphenotypic plasma cells, lymphocytes, and histiocytes in a background of mild edema, myxoid matrix, and proliferation of loosely arranged stellate, polygonal or spindle shaped myofibroblasts, (b) fascicular, characterized by compact fascicles or storiform bundles of spindle cells, again with inflammatory cell infiltrate in the background, (c) hypocellular fibrous composed of dense collagen fibers, scarce spindle cells, and inflammatory cells.

Myofibroblasts are mesenchymal cells that appear spindle shaped (bipolar), or stellate by light microscopy. The nuclei are elongated, tapered or wavy, pale, with tiny small central nucleolus. The 2 types of cells that closely resemble the myofibroblasts by light microscopy are the fibroblast, and the smooth muscle cell. Fibroblasts appear either spindle shaped with tapered ends (inactive state), or plump (active state). Smooth muscle cells exhibit elongated nuclei with blunt ends (cigar shaped), and abundant spindle shaped eosinophilic cytoplasm.

Demonstration of ultrastructural features is the only certain way to confirm myofibroblastic differentiation. However, one of the major features (the fibronexus, which is a specific cell to stroma attachment) that differentiates the myofibroblast from its look alike (the fibroblast and the smooth muscle cell), is often absent in neoplastic cells.[8] Myofibroblasts are currently identified based on morphology (regular hematoxylin and eosin stained tissue section), and on the expression of at least one myoid differentiation antigen (Actin, Desmin)[8]

The cause of systemic B type symptoms seen in IMT is unknown. However, overproduction of the cytokine interleukin 6 (IL-6) was demonstrated.[4]

The prediction of the clinical behavior of IMT has been elusive. In 1991, Meis and Enzinger[9] reported a series of 38 cases of myofibroblastic proliferation with a high rate of local recurrence, locally aggressive behavior, and distant metastases.[9] The cases were considered to be low grade sarcomas, and the researchers proposed the use of the term "inflammatory fibrosarcoma," in order to convey this message to the clinicians. However, there was too much overlapping between the clinical and histological features of these cases and those reported as indolent in the literature.

There are currently no definitive clinical, histopathologic, cytogenetic, or molecular criteria to accurately predict locally aggressive behavior, or distant metastases at the time of initial excision of an IMT.[2,3] Inflammatory myofibroblastic tumor and "inflammatory fibrosarcoma" are viewed as a single entity in the WHO classification of soft tissue tumors.[6]

The histological differential diagnosis includes: sarcomatoid carcinoma (carcinoma composed of spindle shaped mesenchymal-like cell), desmoid tumor (aggressive fibromatosis), sclerosing mesenteritis, gastrointestinal stromal tumor (GIST), Schwannoma, leiomyoma, leiomyosarcoma, follicular dendritic cell tumor, solitary fibrous tumor, well differentiated inflammatory liposarcoma, sarcomatoid mesothelioma, and mycobacterial spindle cell pseudotumor.

Typhoid fever (enteric fever) is still an endemic disease in Lebanon.[10-12] Bacteriological culture (blood, bone marrow, stool, or urine) is the gold standard for definitive diagnosis.[13] Its sensitivity varies between 73% and 97%, if multiple blood cultures are obtained.[13] Blood culture was negative in the current case.

Widal test is a serology test whose function is to detect the presence of antibodies directed against the somatic antigen (O), and the flagellar antigen (H) of *Salmonella typhi*. A test performed twice (paired test; acute and convalescent samples) at 2-3 week interval, in search for a fourfold, or higher increase in the titer (rather than for a single absolute value), is the widely accepted and recommended approach for a serology based diagnosis.[13] However, this approach seems to have little practical value. Patient management decisions cannot be postponed until the results of the convalescent sera are available, and the physicians most often have to make decisions based on a single tube (unpaired) agglutination test. False positive Widal test results have been reported in association with infections with other bacteria, especially members of the family of *Enterobacteriacea,*[13] malaria,[14] tuberculosis,[15] rheumatoid arthritis,[13] and chronic liver disease.[13]

In 2 previous studies, looking into the clinical characteristics of typhoid fever in Lebanon, and the usefulness of a single Widal test for a positive diagnosis, Hamze et al,[11] and Tohme et al[12] concluded that in the appropriate clinical context, and despite its well known limitations - a single Widal test with an agglutinin O titer of 1/160 or higher, remains a valuable and reliable diagnostic tool for the diagnosis.

The patient in this case complained of remittent high-grade fever of long duration, in association with cough, both of which are known to occur in typhoid fever.[13] He did not have leukopenia, which is reported in 16-46% of cases.[13] Leukopenia was not a helpful diagnostic marker in a clinical study on 70 patients conducted in Lebanon.[12] Despite a negative blood culture, a diagnosis of typhoid fever was made based on the clinical presentation, and on the data obtained from the previously mentioned Lebanese studies.[10-12] The association of a single positive Widal test (TO: 1/160; TH: 1/320) (in the context of prolonged high fever in a known endemic area) with the presence of mesenteric IMT, was not, to our knowledge, previously reported in the literature. The probability that the 2 conditions are completely unrelated, and that the association is a mere coincidence, cannot be excluded. Inflammatory myofibroblastic tumor occurs mostly in this age group, and the mesentery is the most affected organ after the lungs.[2,3] The patient lives in an area where *Salmonellosis* is frequent, and a positive Widal test (true or false) is not uncommon. However, it is obvious that the tumor was directly responsible for the fever, as well as for the other systemic abnormalities (elevated ESR, anemia, thrombocytosis), because all parameters (including fever), returned to normal within a short period after the surgery (24-48 hours), which is a well documented phenomenon in IMT.[2,4] Given the negative blood culture and the known limitations of a single (unpaired) Widal test, a definitive unequivocal diagnosis of typhoid fever cannot be rendered in this case.

We favor the hypothesis that Widal test was falsely positive, most likely due to the polyclonal hypergammaglobulinemia known to be associated with IMT.[2] Polyclonal hypergammaglobulinemia (as occurs in rheumatoid arthritis and cirrhosis), is one of the causes of a false positive Widal test.[13]

In summary, we report a case of mesenteric IMT, associated with a positive Widal test (TO: 1/160; TH: 1/320), within a clinical context that is highly suspicious for typhoid fever. Physicians, especially pediatricians practicing in endemic areas, should be aware of this mimicry.

The search for, and the study of possible similar case scenarios in the future are needed, in order to shed some light on this issue, and to show whether there is actually a link between IMT and positive Widal, or is it a simple coincidence of 2 completely unrelated diseases, both of which are frequent in this age and living conditions.

Given the absence or extreme scarcity of typhoid fever in Western societies, epidemiologic studies conducted in areas where the disease is still endemic, have much more chance to yield statistically significant data.

Acknowledgment. *We would like to thank Dr. Alhan A. Jebai for the Arabic translation of the abstract.*

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Case Reports

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