A rare case of fever of unknown origin : Inflammatory myofibroblastic tumor of the liver. Case report and review of the literature

Jens Kruth[1], Henrik Michaely[2], Markus Trunk[3], Marco Niedergethmann[4], Ann-Katrin Rupf[5], Bernhard K. Krämer[6], Uwe Göttmann[6]

(1) 3rd Department of Medicine (Hematology and Oncology) ; (2) Department of Clinical Radiology and Nuclear Medicine ; (3) Department of Pathology ; (4) Department of Surgery ; (5) 2nd Department of Medicine (Gastroenterology/Hepatology) ; (6) 5th Department of Medicine (Nephrology/Endocrinology/Rheumatology), University Hospital Mannheim, University of Heidelberg, Mannheim, Germany.

Abstract

We present the case of a rare cause of fever of unknown origin (FUO). FUO is challenging for patients as well as for physicians as there are more than 200 differential diagnoses of FUO (1,2). Pointing out a diagnosis often requires numerous noninvasive and invasive procedures that sometimes even fail to explain the fever. Our patient was admitted twice to our hospital due to remitting fever rising up to 40°C without any subjective discomfort. At the first presentation no clinical focus could be identified. This included the examination of multiple blood and urine cultures, serology, autoimmune serology, transesophageal echocardiography, CT-scan of the lung and the abdomen, and bone scintigraphy. Elevated C-reactive protein (268 mg/l) decreased spontaneously and fever disappeared after 4 weeks. However, the patient was re-admitted 4 months later with identical symptoms. Multiple blood and urine cultures, serology, bone marrow examination, CT-scan of the lung and the abdomen, esophago-gastro-duodenoscopy and colonoscopy still showed no pathological findings. MRI-scan of the abdomen identified a liver tumor of 3.3 cm in diameter in segment 6 without typical signs of an adenoma, focal nodular hyperplasia or hepatocellular carcinoma. Biopsy of the suspect liver lesion revealed an inflammatory myofibroblastic tumor (inflammatory pseudotumor). After surgical resection of the tumor elevated inflammation markers as C-reactive protein normalized and fever disappeared. One year after surgery no more episodes of fever re-occurred.

An inflammatory myofibroblastic tumor of the liver can be a rare cause of fever of unknown origin. MRI-scan can be an additional imaging tool to identify previously not recognized liver tumors. (Acta gastroenterol. belg., **2012**, 75, **448-453**).

Key words : inflammatory myofibroblastic tumor, inflammatory pseudotumor, fever of unknown origin, liver tumor.

Anamnesis

A 41-year old female patient was admitted for the first time because of continua-type fever rising up to 40°C. The fever persisted for three weeks and was treated with antibiotics (levofloxacine and cotrimoxazole due to dysuria) by the family doctor without success. Additionally, night sweat, shivering, and fatigue during fever were present. The past medical history gave no clue in regards to travelling, contact with infected animals, infection by parasites, drug abuse or infected family members. Chronic diseases, smoking, regular alcohol consume or medication were denied. No surgery had been performed previously. She had three children and was working as a consulting-room assistant in an ORL practice. During the diagnostic investigation (see below) she spontaneously experienced a complete remission and could be discharged in a good condition. Unfortunately, 4 months later fever re-emerged and was present for two weeks at the second admission. Again she was temporarily unable to work due to malaise.

Physical examination and clinical findings

At both admissions, the patient was in a good clinical and mental condition (160 cm, 90.6 kg, BMI 35 kg/m^2). Blood pressure was 120/60 mmHg, heart rate was 105/min and body temperature was 38.6°C. Beyond that there were no objective suspect clinical signs, in particular no exanthema, lymphadenopathia, enlarged palpable or sensitive liver or spleen, respectively, or cardiac murmurs.

Diagnostic investigation

At first admission, the diagnostic procedures were aimed for searching an infectious, an inflammatory, or a malignant origin of the patient's complains.

Pathological findings in blood tests and urine examination were as follows (normal value) : potassium 3.42 mmol/l (3.6-4.8), albumin 28.6 g/l (35-52), gamma glutamyltransferase 90 U/l (0-40), alanine aminotransferase 47 U/l (0-35), aspartate aminotransferase 57 U/l (0-35), leucocytes 16.369/ul (4200-10200), C-reactive protein 263 mg/l (0-5) (Fig. 1), pro-calcitonin 1,54 ug/l (0-0.2), microalbuminuria 602 mg/l (0-20) and proteinuria 935 mg/l (0-150). Of note, pro-calcitonin level as a marker for bacterial infection was elevated. Nevertheless, blood cultures and urine specimen analyses could not identify any microbial pathogen responsible for the fever. There were no pathological findings in serology, i.e. hepatitis virus A, B, C, cytomegalovirus, parvovirus, Q-fever and borrelia burgdorferi. Markers for autoimmune disorders showed no abnormalities (ANA,

Correspondence to : Jens Kruth, M.D., 3rd Department of Medicine (Hematology and Oncology), University Medical Centre Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68135 Mannheim, Germany.
E-mail : jens.kruth@web.de

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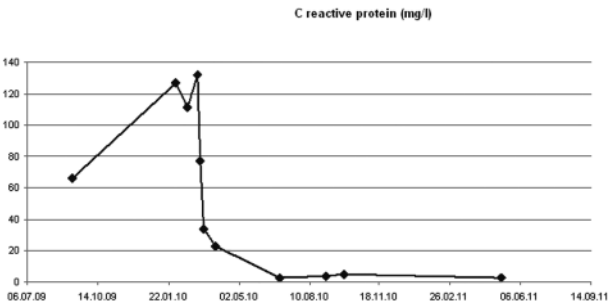

Fig. 1. — C-reactive protein levels (mg/l) over time

ENA, anti-dsDNA, ANCA, liver specific autoantibodies, anti-CCP-antibodies, rheumatoid factor, complement levels C3, C4, CH50). Sonography of the abdomen and lymph nodes, scintigraphy of the bones as well as contrast-enhanced computed tomography (CT) of the lung and the abdomen could not show any signs of tumor or infectious focus, respectively. A transesophageal echocardiography showed a physiological cardiac status. Oesophagogastroduodenoscopy and colonoscopy were also unrevealing.

Clinical course

The patient showed a complete spontaneous clinical remission and could be discharged without medication. She was without any complains for approximately four months. At second admission she again had fever up to 40°C for about 10 days. In contrast to the first admission she now also suffered from increasing movement dependent pain in the proximal limbs without any signs of exanthema or elevated serum muscle enzymes. A bone marrow biopsy and a second whole body CT scan were performed. Accidentally, a young assistant radiologist described a liver cyst (segment 8) in the CT scan as suspect (which was revised later on by the senior physicians and diagnosed as a simple liver cyst), so that an additional MRI-scan of the abdomen was performed (Fig. 2A-D). As a coincidence, a further liver lesion was identified in segment 6 that was previously undetected by contrast-enhanced CT imaging beforehand. The lesion displayed no typical sings of an adenoma, focal nodular hyperplasia or hepatocellular carcinoma. Using the data of tumor position (obtained by the previous MRI-scan) a subsequently performed CT-guided biopsy of the liver lesion showed on histopathological examination a polymorph infiltration of plasma cells, neutrophil, and eosinophil granulocytes with mesenchymal inflammation (Fig. 3A+B). There were no immunohistopathological signs of carcinoma, lymphoma and myeloma, respectively. The liver tissue showed a highly increased staining for actine as an activity marker. The Ki-67 associated proliferation index (MIB-1) within the tumor was 5-10%. CMV and EBV proteins were not detectable in this tumor. With regard to the histopathology our patient displayed an inflammatory myofibroblastic tumor of the liver.

Due to the remittent fever episodes and after thorough discussion with the patient we recommended a complete surgical resection of this liver lesion. Reasons were the patient's young age, unknown spontaneous clinical course, and the probable need of long-term treatment with corticosteroids. The post-surgical course was uneventful. The fever as well as all serological markers of inflammation decreased to physiological values, including absolute numbers of C-reactive protein (Fig. 1), leucocytes, and blood sedimentation rate. One year after resection our patient still had no fever and has had no other complaints.

Discussion

Our patient had fever reaching up to 40°C persisting for several weeks twice. Careful physical examination revealed no pathological findings and history regarding travelling, animal exposure, drug, and toxin history was uneventful. Initial laboratory testing pointed towards a bacterial disease as we found elevated levels of C-reactive protein (263 mg/l) as well as pro-calcitonin (1.54 µg/l). Despite an extensive work-up no infectious focus could be located. A rheumatologic disease as cause of FUO could not be elucidated as autoimmune-serology was negative and clinical signs of vasculitis or collagenosis were not present. Although the patient underwent a contrast-enhanced CT scan of the thorax and abdomen on both admissions and a bone marrow examination was done, no solid tumor or evidence for a hematologic malignant disease could be found. Additional MRI-scan of the abdomen revealed a liver tumor in segment 6, which was identified as an inflammatory myofibroblastic tumor on diagnostic CT-guided biopsy.

In the following we will give a short overview of fever of unknown origin and the rare cases of inflammatory myofibroblastic tumors.

Fever of unknown origin

In 1961 Petersdorf and Beeson first provided a definition of fever of unknown origin (FUO) in an analysis of 100 cases. It includes fever higher than 38.3°C on several occasions lasting for at least three weeks with an uncertain diagnosis after one week of examination in the hospital (3). Over the past decades health care has shifted from the inpatient to the ambulatory setting and as a result it has now become widely accepted that medical evaluation can be performed in an outpatient setting as well to fulfill the criteria for FUO (4). An expansion of the definition of FUO to include nosocomial, neutropenic, and HIV-associated fevers has been recently suggested (5,6). To make a statement about the epidemiology and etiology of FUO one has to consider that *a)* true FUO is rare (7), *b)* different definitions of FUO

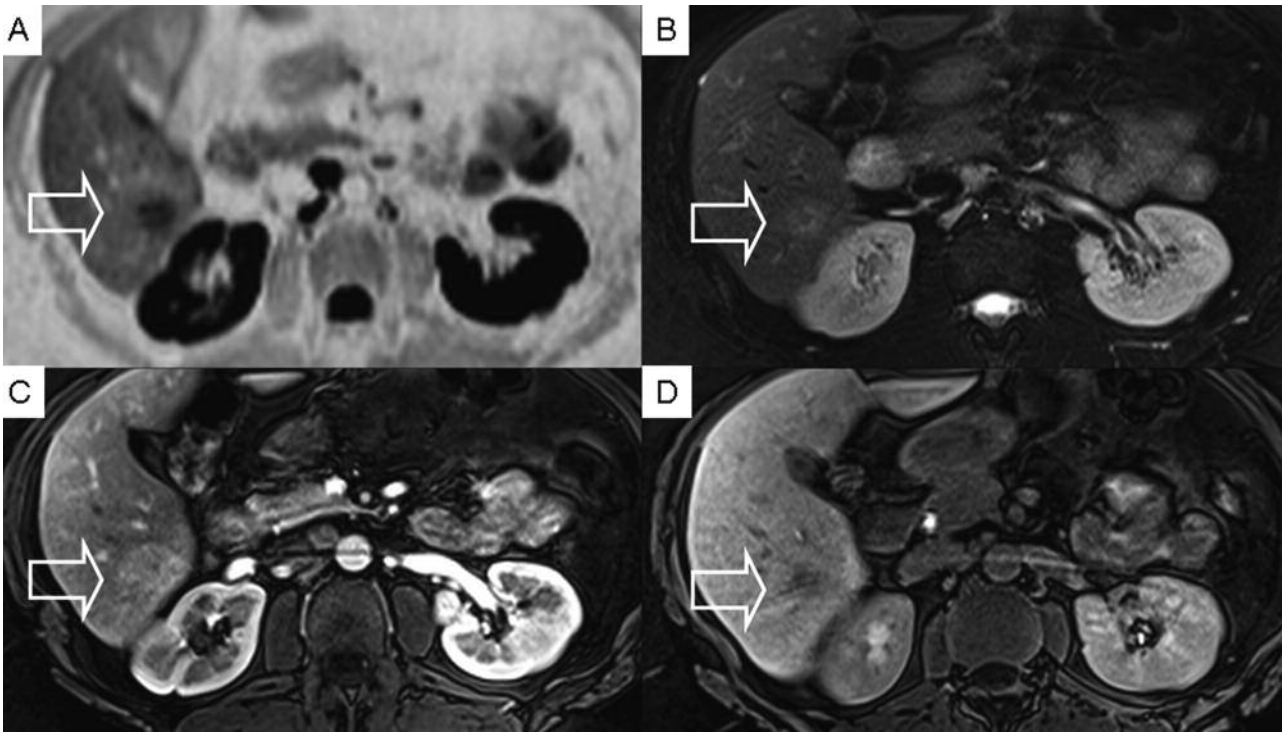

Fig. 2. — Exemplary axial MRI-images of the inflammatory pseudotumor (arrows) acquired at 3.0T.
A. Diffusion-weighted sequence (b = 800 mm/s) demonstrating the tumor as a well circumscribed lesion in the segment 6 of the liver. B. In the T2-weighted TSE sequence with fat suppression the tumor is barely seen as slightly hyperintense focal lesion. C. The arterial phase T1-weighted 3D-VIBE sequence after the administration of Gd-EOB-DTPA demonstrates a slightly hypervascularized lesion occupying a larger territory than in the non-enhanced sequences. D. In the hepatocyte-specific late phase 20 minutes after Gd-EOB-DTPA injection homogeneous enhancement of the liver can be appreciated while the ill-defined tumor demonstrates a reduced uptake of the contrast agent. Not shown are contrast-enhanced CT-images on which the tumor could not be depicted.

have been published in the literature (8), *c)* geographical differences in etiology, incidence, and medical standards exist (i.e. developing world) (9), and *d)* etiology and incidence varies with age and subgroups studied (HIV, immunosuppression, neutropenia) (10,11).

With over 200 differential diagnoses reported FUO is challenging for patients and physicians alike (1,2) and finding a diagnosis often requires numerous noninvasive and invasive procedures which sometimes still fail to explain the fever. Despite of the heterogeneous causes and origins, there are no guidelines for a diagnostic workup of FUO. To meet up with the requirements of a target-oriented and medical resource saving diagnostic workup one should have a look at the most common causes of FUO. The differential diagnoses of FUO can be classified into four categories : infections, malignancies, noninfectious inflammatory diseases (e.g. autoimmune disorders), and miscellaneous. Reports of series including more than 1000 patients with FUO published between 1952-1994 revealed that the spectrum of the responsible diseases include infections in 28%, malignancies in 17%, non-inflammatory diseases in 21% and never identifiable causes in 19% (12). A recent study report from 6 Dutch hospitals identified only 73 patients fulfilling the diagnostic criteria of FUO (7). The distribution of causes were infections in 16%, malignancies in 7%, non-inflammatory diseases in 22%, never-identified causes in 51%, and miscellaneous in 4%. In this study, the advances in imaging techniques (CT, MRI, sonography) during the last decades most probably resulted in a better detection of solid tumors or abnormal lymph nodes leading to a decrease of tumors as a common cause of FUO.

Regarding infections, tuberculosis remains the most common cause of FUO followed by intra-abdominal abscesses (3,8,13-15). Diagnostic work-up to rule out infectious endocarditis should include transesophageal echocardiography and collection of at least three blood cultures taken at different points in time. One should keep in mind that the detection of several microorganisms e.g. of the HACEK-group requires longer incubation of blood cultures. Diagnostic work-up should consider the different spectrum of microorganisms found in patients with different etiology of FUO i.e. in patients under immunosuppression and neutropenic patients.

The most common malignancies in patients with FUO are Hodgkin's disease and non-Hodgkin's lymphoma (8, 13), but many other tumors, i.e. renal cell carcinoma,

liver tumors, colon carcinoma or lung cancer have been described as causative factors for FUO as so called "neoplastic fever" (16). Fever during cytoreductive therapy associated with neutropenia is mostly caused by infections but neutropenic FUO can occur as well. In these cases the physician is confronted with a difficult situation as causative factors can include rare pathogens, fever induced by chemotherapeutics (e.g. cytarabine, bleomycine, cisplatine, and immunomodulators like interferon) or by the tumor itself.

Non-inflammatory diseases represent approximately 20% of patients with FUO. In middle-aged persons adult Still's disease and giant cell arteriitis in older individuals are the most common rheumatologic disorders presenting with FUO. Giant cell arteriitis accounts for 15-17% of FUO in the elderly (1,17). Other rheumatologic disorders, which can cause FUO, include polyangiitis nodosa, Takayasu's arteriitis and Wegener granulomatosis.

Inflammatory myofibroblastic tumor/Inflammatory pseudotumor

Inflammatory myofibroblastic tumors (IMT) have also been named inflammatory pseudotumors (IPT) and the terminology used in the literature has varied in the last decades (18). They primarily occur during the first decades of life. Typical locations of IMT in adults are the lung, retroperitoneum or the abdominopelvic region (19), whereas in children urinary or gastrointestinal IMTs have been reported to be twice as frequent as pulmonary IMTs (20). Unusual locations have been described in the literature including spinal cord, brain, heart, bone or adrenal glands. Since the first description in 1953 (21) IMTs of the liver are increasingly recognized, most likely due to better imaging techniques. IMT represent a rare differential diagnosis of liver masses found in 1% of 403 patients who underwent liver resection for focal liver lesions (22).

Histological IMTs are classified as intermediate neoplasms in the World Health Organization's classification of histological typing of tumors of soft tissue and bone (23). Different cell types can be found in IMTs with myofibroblasts representing the majority of cells (19). They are generally incorporated into a myxoid to collagenous stroma admixed with inflammatory cells. Sometimes variable inflammatory plasmacellular infiltrates with extravasating erythrocytes and eosinophilic granulocytes can be found. Apart from the inflammatory lesions sclerosis tissue can be detected in IMTs (24). Immunohistochemical spindle cells found in the tumor express smooth muscle actin in nearly 90% of the cases, desmin can be detected as well but with a less intensity. Cytoceratins can be found in IMT of mesenteric origin in some cases and CD68 is found in macrophages and spindle cells in nearly 25% (24). Recent studies have shown that rearrangements involving the ALK locus on chromosome 2p23 have been documented in about 50% of IMTs (25,26) and that treatment with the ALK inhibitor crizotinib resulted in a sustained partial response in a patient with ALK-translocated IMT of the liver and omentum (27).

There are no specific signs to diagnose IMT in CT or MRI-scans (28). The spectrum of presentation is wide and IMTs are often misdiagnosed as hepatocellular carcinoma. CT appearance ranges from low density lesions with irregular delayed enhancement to peripheral enhancement in early phases of dynamic CT (29,30). MRI can reveal different patterns from layered patterns of contrast enhancement during dynamic imaging, consisting of outer hypovascular zones and inner hypervascular stroma, mimicking the imaging features of pyogenic organized abscess with deficient central necrosis. T3 weighted images mostly show hyperintensity, suggesting immature fibrosis corresponding to the area of arterial hypovascularity and delayed contrast enhancement (31). In our case the inherently higher soft tissue contrast of MRI facilitates the displaying of the tumor. Particularly the addition of DWI-imaging improves diagnostic accuracy as this sequence provides a molecular contrast defined by the Brownian motion, which is suppressed in cell-rich tumors (32).

Management of IMTs remains controversial, with some physicians favouring a conservative approach using antibiotics, steroids or NSAR and others favouring a surgical resection (28,33). The optimal management certainly depends on the size and the location of the tumor and the existence of metastatic disease. Whenever possible a histological diagnosis should be made before starting treatment. In IMTs with ALK expression, treatment with the ALK inhibitor crizitonib may be useful in cases that are complicated by local recurrences or in cases of unresectable IMTs facilitating their complete surgical removal (27). However, the approach of treatment of IMT of the liver is controversial in the literature. This is demonstrated by a review of 188 cases of inflammatory pseudotumors of the liver (28). Of these 188 patients, 56% underwent a liver resection whereas 40% were managed conservatively. Patients who underwent a diagnostic liver biopsy were more likely to be treated conservatively as a histological diagnosis was available. In this retrospective series there was no difference in the mortality rate of patients managed conservatively and those who underwent a liver resection, but data was not adjusted for confounders such as i.e. age, tumor size, tumor location or metastatic disease.

Regarding our patient we recommended the resection of the tumor in accordance with our local hepatobiliary surgeons due to the following reasons : First, IMTs are soft tissue tumors of intermediate biological potential of malignancy with a small fraction behaving aggressively (34). Some authors even assume that IMTs and the rare malignant variants of inflammatory fibrosarcoma are histogenetical related lesions which may eventually display different spectra of a malignant disease with a relevant metastatic potential (18,24,35). Second, a serious complication of many chronic inflammatory disorders is systemic AA amyloidosis (36). It is noteworthy

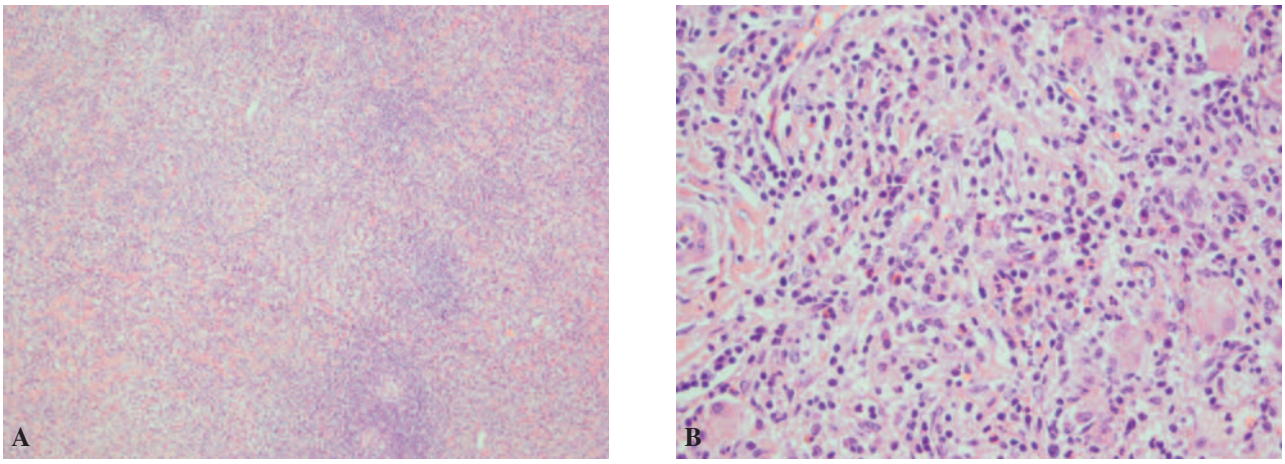

Fig. 3. — Light microscopy of the resected IMT shows a polymorph infiltration of plasma cells, neutrophilic and eosinophilic granulocytes with mesenchymal inflammation. Hemotoxylin-eosin staining, magnification 4× (A) and 20× (B).

that after surgical resection of the tumor elevated inflammation markers as C-reactive protein normalized within a few weeks and fever disappeared. One year after surgery the patient still shows no clinical symptoms or any pathological findings in blood tests.

In summary, IMTs of the liver can be a rare cause of FUO. As the presented IMT was not apparent in the contrast-enhanced CT scan, additional MRI of the abdomen should be considered in such cases as it can be helpful in identifying primarily not visible tumors.

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