



## ULTRASOUND EXPLORATION IN THE WORK-UP OF UNEXPLAINED FEVER IN THE IMMUNOCOMPROMIZED HOST: PRELIMINARY OBSERVATIONS

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### ABSTRACT

In immunocompromized hosts, febrile episodes have an unknown origin (FUO) in about fifty per cent of cases. In this preliminary study we evaluated the role of abdominal and pleural ultrasound (US) examination for early detection of infectious sites. US exploration was performed in a cohort of 14 consecutive FUO patients early after fever onset, at patients' bedside, by a hematologist trained in diagnostic ultrasound, and it was repeated at neutrophil recovery. US exploration showed abnormal abdominal findings in 7 and

pleural effusion in 3 patients. In all cases but one the abnormality was found at the first US examination. Abdominal and pleural US exploration is a low-cost, easy to use tool for the work-up of FUO in the immunocompromized host that proved to be effective in identifying the infection site in about 50% of patients.

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Infectious complications in patients with hematological malignancies are associated with high morbidity and mortality.<sup>1</sup> Severe and prolonged neutropenia, deficit of cell-mediated immunity, drug-induced mucosal damage, presence of central venous catheter and acute or chronic graft versus host disease are well-known risk factors and are often combined in the same patient.<sup>2</sup> In immunocompromized patients, febrile episodes can be defined as clinically documented infections (CDI) in 24% of cases and microbiologically documented infections (MDI) in 30% of cases; in the remaining 46% the fever has an unknown origin (FUO).<sup>3,4</sup> At present, the minimum initial work-up suggested for patients with FUO involves physical examination, a battery of laboratory tests including blood, urine and stool cultures, and a chest X-ray.<sup>2</sup> If the fever persists, arterial blood gas analysis, fundus oculi examination, cranium X-ray and ultrasound (US) exploration are often recommended.<sup>5,6</sup> With the aim of defining the location and, when possible, the etiology of the fever earlier and better, we added abdominal and pleural US exploration to the initial work-up in a cohort of consecutive patients with FUO, even in the absence of local symptoms.

### Materials and Methods

From September to December 1996 we studied 14 immunocompromized patients who experienced a febrile episode (> 38°C) that was unresponsive to at least four days of empiric antibiotic therapy. In addition to the standard work-up (physical examination, laboratory tests, cultures, chest X-ray, histocy-

tological examination if clinically indicated), an US study was performed between the 4th and 6th day of fever at the patient's bedside by a hematologist trained in diagnostic ultrasound, using portable Spazio-Hitachi equipment with a 3.5 Mhz probe. The exploration was repeated at neutrophil recovery (10-20 days later).

### Results

US exploration showed abnormal abdominal findings in 7 of the 14 patients studied; pleural effusion was detected in 3 patients and particulate peritoneal fluid in 2 (Table 1). The abnormality was detected at the first US examination in all cases but one (case #12), thus changing the diagnosis from FUO to CDI (or to MDI when a fine needle aspirate biopsy could be performed). Two cases of moderate pleural effusion had not been detected at chest X-ray; a CT scan failed to reveal choledochal lithiasis in one patient and could not document that a peritoneal effusion was particulate in another. A few representative cases are detailed below.

Case #7. A 31-year-old man with acute promyelocytic leukemia was receiving the first consolidation course of the AIDA protocol when fever appeared, associated with moderate pain in the left lower abdominal quadrant where a scar, related to previous surgery for nephrostomy, was present. Physical examination was non contributory. US examination showed a large hypoechoic image (10 cm) (Figure 1), just under the scar. A CT scan confirmed the lesion. A culture of the fluid obtained through fine needle aspiration showed *Pseudomonas*

**Table 1. Patient characteristics.**

Pt.	Age, sex	Basic disease	US scan	Diagnosis
1	75F	CML-BC	Intrasplenic hypo-echoic images likely due to localization of the hematological disease	Non-infectious fever
2	34F	ALL	None	MDI (sepsis)
3	61M	AML	None	FUO
4	42M	AML	None	MDI (sepsis)
5	54M	AML	Pleural effusion	CDI (lung)
6	35M	NHL	Particulate peritoneal and pleural effusion	CDI (serositis)
7	31M	APL	Pelvic abscess	MDI
8	60M	CMML	Particulate peritoneal and pleural effusion, hydronephrosis	CDI (serositis)
9	66F	LLC	None	FUO
10	16M	NHL	None	CDI (lung)
11	73F	RAEB	Biliary duct dilatation	Cholangitis, biliary lithiasis
12	48M	AML	Solid intrasplenic image	CDI (lung, spleen)
13	25F	AML	Ileal loop thickening	Ileotyphlitis
14	39M	APL	None	FUO

AML= acute myeloid leukemia; APL= acute promyelocytic leukemia; NHL= aggressive non Hodgkin's lymphoma; ALL= acute lymphoblastic leukemia; RAEB= refractory anemia with excess blasts; CLL= chronic lymphocytic leukemia; CMML= chronic myelo-monocytic leukemia; CML-BC= chronic myeloid leukemia in myeloid blast crisis; CDI= clinically documented infection; MDI= microbiologically documented infection; FUO= fever of unknown origin; M=male; F= female.

*aeruginosa* and *Klebsiella pneumoniae*. The patient recovered after specific antibiotic treatment and surgical drain.

Case #11. A 73-year-old woman with RAEB presented with fever, no abdominal pain, moderate transaminase elevation and increased bilirubin, alkaline phosphatase and  $\gamma$ -glutamyl transferase (5 x n.v.). Liver US examination revealed intra- and extrahepatic duct dilation with choledochal lithiasis. The abdominal CT scan was negative.

Case #12. A 48-year-old man with AML-M4 was in post-induction aplastic phase. After ten days of intense neutropenia, he developed fever and signs of respiratory tract infection. A CT scan revealed an excavated lesion in the right lung; US scan was negative at that time. At neutrophil recovery, a repeat US examination showed a normal-sized spleen with an intrasplenic solid spherical image (3 cm) and hypoechoic contour. A CT scan confirmed the lesion. A needle aspirate could not be performed because of thrombocytopenia. The splenic lesion was considered as a consolidated splenic abscess, and in fact it disappeared following antibiotic treat-



**Figure 1. Left lower abdominal quadrant US scan showing a roughly spherical hypoechoic image with internal echoes and an irregular contour (case # 7: pelvic abscess).**



**Figure 2. Ultrasonographic images of ileotyphlitis (case # 13). A: superdistended ileum with hematic fluid in the lumen. B: ileal loops with thickening of the wall.**

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Case #13. A 26-year-old woman had received induction treatment for AML. After 10 days of neutropenia she presented fever, vomiting, hematic diarrhea (WHO grade 3) and abdominal pain in

the right lower quadrant. US scan visualized a superdistended ileum containing fluid (Figure 2A) and intestinal loops with thickening of the wall (Figure 2B), typical of ileotyphlitis. A CT scan confirmed these findings without adding further information. Following appropriate anti-infective treatment, clinical and instrumental examinations were brought back to normal in three weeks.

### Discussion

Under optimal study conditions and with an experienced operator, modern US equipment allows accurate exploration of liver, biliary tract, spleen, pancreas, kidneys, gastrointestinal tract, main vascular routes, lymph nodes and pleural cavities,<sup>7</sup> even at bedside using portable equipment. We think that US exploration is a rapid, safe, effective and low-cost instrumental examination for patients with FUO. Until now, it has been used mainly in febrile patients with the aim of detecting possible mycotic hepatic or splenic lesions,<sup>5,6</sup> which usually appear late in FUO patients at neutrophil recovery. Our preliminary study demonstrates that early use of ultrasonography may be valuable for precocious detection of the site of infection, thus facilitating more thorough investigation and ultimately leading to more appropriate treatment.

In our small series, we demonstrated that abdominal and pleural US examination can move a number of patients from FUO to CDI, or even to MDI, when a needle aspirate is indicated and can be performed. We suggest that hematological units keep a portable US equipment available and have it run by an experienced operator, who could be a member of the hematological staff trained in diagnostic ultrasonography.

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