Role of Diagnostic Splenectomy in Patients Presenting with Pyrexia of Unknown Origin with Splenomegaly and Non-Contributory Pre-surgical Evaluation

Muralidharan J1, Ralph R2*, Mathuram A3, Prakash V4, Nayak S5, Zachariah A3

Abstract

Aims: To describe the clinical and laboratory profile, post-surgical complications and longitudinal outcomes in a historical cohort of pyrexia of unknown origin (PUO) patients with splenomegaly who underwent a diagnostic splenectomy following non-contributory extensive pre-surgical laboratory and radiological evaluation.

Materials and Methods: This retrospective study was conducted in a 2700 bed teaching hospital in South India, in eligible patients, over a 10-year period.

Results: Out of 38 PUO patients who underwent diagnostic splenectomy, a final diagnosis was established in 30 patients. Overall, infections contributed to 44% (13/30), and neoplasia to 56% (17/30) of all cases. Of PUO patients with infections 3/13 (23%) were diagnosed with disseminated tuberculosis, 7/13 (54%) with melioidosis, 1/13 (8%) with Candida splenic abscess with infective endocarditis and 2/13 (15%) with Colistin-resistant E. coli splenic abscess. Amongst PUO patients with neoplasia (17/30), all patients were diagnosed with hematological neoplasia. Of these 94% (16/17) were diagnosed with Non-Hodgkin’s lymphoma and 6% (1/17) with Hodgkin’s disease. Splenectomy was non-contributory in 21% (8/38) patients. Post-operative complications were seen in 6/38 patients who required monitoring in the intensive care unit (ICU). In-hospital mortality was noted in 10.5% (4/38) patients.

Conclusions: Diagnostic splenectomy has high diagnostic utility in the evaluation of PUO patients with reticuloendothelial system involvement after an extensive negative investigative workup. The diagnosis of lymphoma in such patients is more common than an infective cause.

Introduction

Pyrexia of unknown origin (PUO) remains a diagnostic challenge to the physician. The Durack and Street classification defines classical PUO as fever greater than 101°F on several occasions for more than three weeks and failure to reach a diagnosis despite one week of in-patient investigation. The true incidence and prevalence of pyrexia of unknown origin remains uncertain. Broadly, causes may be divided into infections, neoplasia or connective tissue disease. Indian studies show that despite detailed clinical and investigative evaluation, up to 27% of PUO patients remain undiagnosed.

With the advent of modern interventional radiological techniques today, more invasive investigations like diagnostic laparotomy and splenectomy have been relegated to the last line of a series of tests for PUO evaluation. However, in the patient subset that remains undiagnosed despite extensive laboratory and radiological investigations, surgical exploration may assume a more significant role. Furthermore, in PUO patients with associated splenomegaly, diagnostic splenectomy may contribute significantly to establishing the etiological diagnosis.

A 2008 Chinese retrospective review of the medical records of 54 PUO patients with splenomegaly, who subsequently underwent a diagnostic splenectomy, revealed that a definite etiological diagnosis was made in 72.2% of patients. A similar study conducted at a Chinese tertiary care center in 2017, involving 83 PUO patients with splenomegaly scheduled for a diagnostic splenectomy following non-contributory initial evaluation, revealed that a definitive etiological diagnosis was made in 89.2% (74/82) of patients. Given the paucity of information from India, we set out to study the diagnostic role of splenectomy and its associated complications, in a historical cohort of Indian PUO patients with splenomegaly and a non-contributory preliminary laboratory and radiological evaluation.

Material and Methods

This study was conducted in a historical cohort of classical PUO patients with splenomegaly, admitted for diagnostic splenectomy, between March 2006 and March 2016 at a tertiary care referral center in South India, receiving an average of 2500 inpatients and 8000 outpatients/day. The predominant catchment area for the hospital includes the districts of Vellore and Tiruvannamalai in Tamil Nadu state and Chittoor district of Andhra Pradesh. The study was approved by the institutional review board and the human research ethics committee (Minute No: 10162, May 2017). The study protocol followed the principles of the Declaration of Helsinki.

Inclusion and exclusion criteria

Patients included were aged 18 years or older; had been diagnosed with classical PUO; had a non-contributory pre-surgical etiological work-up and had subsequently undergone a diagnostic splenectomy. Pregnant patients and those with fever related to other PUO categories (nosocomial, neutropenic and HIV-associated) were excluded from the study.

Definitions

Classical PUO was defined according to the Durack and Street criteria as, (1)
an axillary temperature of >38.0°C which corresponds to an oral temperature of >38.3°C; (2) illness duration more than 3 weeks; (3) a lack of a definite diagnosis after three outpatient visits or 3 days in the hospital; (4) fever not related to other categories of PUO (nosocomial, neutropenic and HIV associated).\(^1\)

**Variables and Outcomes**

Clinical information from paper and electronic case records of eligible patients was collected using a systematic data abstraction form. To maintain confidentiality, all patients were assigned a serial number at enrollment. Data was subsequently collected by identifying patients using these serial numbers. Demographics, presenting symptoms and signs, preliminary investigations preceding splenectomy, and outcomes were documented. Pancyclopenia was defined as hemoglobin <10g/dl, white cell count < 4000 cells/cumm and platelet count < 100,000/cumm. Elevated serum transaminase levels were defined as serum glutamic oxaloacetic transferase levels > 40U/L with or without serum glutamic pyruvic transferase levels > 35 U/L.

**Table 1: Demography, clinical profile and laboratory abnormalities**

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=38 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean ± SD)</td>
<td>46.5 (± 16.2)</td>
</tr>
<tr>
<td>Male: Female</td>
<td>21:17</td>
</tr>
<tr>
<td>Duration of febrile illness at admission in months (Mean ± SD)</td>
<td>11.8(±8)</td>
</tr>
<tr>
<td><strong>Presenting clinical features</strong></td>
<td></td>
</tr>
<tr>
<td>Loss of weight and appetite</td>
<td>31 (80)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>22 (58)</td>
</tr>
<tr>
<td>Generalized lymphadenopathy</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Early satiety</td>
<td>18 (48)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>15 (39)</td>
</tr>
<tr>
<td>Splenic abscess (Single/multiple)</td>
<td>16 (42)</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (31.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (29)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td><strong>Presenting laboratory abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Pancyclopenia</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Elevated serum SGOT/SGPT(^1)</td>
<td>7 (18.4)</td>
</tr>
<tr>
<td>Elevated serum ALP(^2)</td>
<td>15 (39.4)</td>
</tr>
<tr>
<td>Elevated serum GGT(^2)</td>
<td>15 (39.4)</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Elevated serum Uric acid(^3)</td>
<td>5 (13)</td>
</tr>
</tbody>
</table>

\(^1\)SGOT (Serum glutamic oxaloacetic transferase), reference range 5-40 U/L; \(^2\)SGPT (Serum glutamic pyruvic transferase), reference range 5-35 U/L, \(^3\)ALP (Alkaline phosphatase), reference range, 40-125 U/L, \(^4\)GGT (Gamma-glutamyl transferase), \(^5\)Uric acid reference range 4-7 mg/dl

The primary outcome was definitive etiological diagnosis post-splenectomy. Secondary outcomes included post-operative complications, post-operative intensive care unit (ICU) admission; length of ICU stay and in-hospital mortality.

**Diagnosis laparotomy**

After obtaining informed consent, a long midline incision was made. Viscera were carefully examined and any suspicious area biopsied. In addition to splenectomy, a wedge biopsy of the liver and sampling of significant intra-abdominal lymph nodes was also performed.

**Statistical analyses**

Data was analyzed using STATA v10.0 (StataCorp, TX, USA). All statistical tests were two tailed. A p value <0.05 was considered significant. Continuous variables were summarized as mean (standard deviation (SD)) if normally distributed or as median with interquartile ranges.

**Results**

Of 230 patients admitted with classical PUO during the study period, 38 consecutive patients (21 males) with splenomegaly and non-contributory pre-surgical etiological work-up were included. The mean age of the study population was 46.5 (16.2) years. 50% (19/38) had febrile illness duration of > 6 months. 15/38 patients were from West Bengal, 8/38 patients from Tamil Nadu, 6/38 patients from Orissa, 4/38 patients from Tripura, 3/38 patients from Jharkhand, 1/38 patients from Kerala and 1/38 from Bihar. Patient characteristics are summarized in Table 1.

Apart from prolonged fever, additional presenting complaints included loss of weight and appetite in 80% (31/38), night sweats in 55% (22/38), nausea and vomiting in 22% (8/38), early satiety in 48% (18/38), generalized lymphadenopathy in 24% (10/38) and hepatosplenomegaly in 39% (15/38). 31.6% (12/38) patients had co-existent diabetes mellitus, 29% (11/38) hypertension, 5.3 % (2/38) chronic liver disease and 2.6% (1/38) chronic lung disease. Common presenting laboratory abnormalities included pancyclopenia in 32% (12/38) and elevated serum alkaline phosphatase with concomitantly elevated serum gamma-glutamyl transferase levels in 39% (15/38) patients (Table 1). None of the patients in this subset had features suggestive of intra-hepatic bile radicle dilatation (IHBRD) on ultrasound abdomen examination.

In addition to CT thorax, abdomen and pelvis; blood culture and sensitivity; and trans-thoracic echocardiography additional diagnostic tests of utility included PET-CT (2/38); bone marrow aspiration and trephine biopsy (35/38); and peripheral lymph node biopsies (10/38). PET-CT imaging revealed multiple intra-abdominal lymph nodes with hepatosplenomegaly with increased FDG uptake in both patients. Subsequent ultrasound guided lymph node biopsies in both patients were non-contributory to the etiological diagnosis. Bone marrow trephine biopsy was repeated from the contralateral iliac bone in 23/38 patients. Image (CT/USG) guided lymph node or lesion biopsy was attempted in 4 patients and ultrasound guided splenic aspiration in 5 patients respectively. The tissue obtained was either insufficient for analysis or non-contributory to the diagnosis both by histopathology and culture. All patients were administered one dose of pneumococcal conjugate vaccine PCV13, one dose of meningococcal polysaccharide vaccine (against Group A, C, Y and W135 strains) and one dose of split virion trivalent inactivated influenza vaccine as intramuscular injections at different sites, at least 2 weeks prior to laparotomy.

A definitive etiological diagnoses based on diagnostic splenectomy was established in 79% (30/38) patients. Overall, infections contributed to 44 % (13/30), and neoplasia to 56% (17/30) of
In 21% (8/38) patients, splenectomy was non-contributory to the etiological diagnosis. Of these, an etiological diagnosis could be established based on liver or lymph node specimens obtained during laparotomy in 3/8 patients. All 3 patients were diagnosed with high grade Non-Hodgkin’s lymphoma. 5/8 patients continued to remain undiagnosed following laparotomy. Their clinical status and reports were reviewed at 6-weeks following discharge.

On review at 6-weeks post-splenectomy, one patient was diagnosed with Non-Hodgkin’s lymphoma based on repeat bone marrow examination done following negative laparotomy. The other 4 patients were contacted via telephone and reported defervesence. They were lost to follow up and could not be examined in person.

Post-operative complications were seen in 6/38 patients who required monitoring in the intensive care unit (ICU). The average ICU stay was 11(± 8.2) days and median ventilator free days at day 28 were 18 (0-28) respectively. In-hospital mortality was noted in 10.5% (4/38) patients (Table 2). Of these, one patient was diagnosed with high-grade Non-Hodgkin’s lymphoma and died of neutropenic sepsis 72 hours post-splenectomy; two patients died of a refractory septic shock possibly secondary to an infected collection in the post-operative surgical site while the fourth patient succumbed to ventilator associated pneumonia. Two patients were noted to have developed incisional hernias on post-operative follow-up at 6-weeks.

### Discussion

Based on the results of our study, there appears to be a low rate of diagnostic splenectomy in PUO patients, with 38 cases over 10 years. The most common clinical profile leading to diagnostic splenectomy in our study population was that of a disease process involving the reticuloendothelial system (hepatosplenomegaly, lymphadenopathy, pancytopenia with liver infiltration), with a non-contributory pre-surgical work-up (bone marrow aspirate smear and trephine biopsy, lymph node biopsy or image guided biopsy of involved sites for histopathological examination and microbiological culture).

Of the patients who underwent the procedure, definitive diagnosis was achieved in 79% (30/38) patients. This finding is similar to that of a 2008 retrospective study on 54 PUO patients with splenomegaly which revealed that definitive diagnosis was made in 72.2% of patients undergoing splenectomy. Diagnostic splenectomy contributed to a diagnosis of hematological neoplasia in more than 50% study patients. A majority of study patients diagnosed with hematological neoplasia had B-cell NHL. None of the patients were diagnosed with any solid organ malignancies.

The most common infectious disease diagnosed based on splenectomy was melioidosis (54%). Tuberculosis was diagnosed in less than 30%, in contrast to the higher prevalence demonstrated in western studies. A possible explanation is that current investigative approaches including culture, molecular diagnosis and guided biopsy are able to achieve an etiological diagnosis in most PUO patients with tuberculosis, seldom requiring a diagnostic laparotomy with splenectomy. Autoimmune diseases such as systemic lupus erythematosus and sarcoidosis did not account for any of the diagnosed cases. This is a surprising observation since these diseases are characterized by prominent reticuloendothelial system involvement. They often present with prolonged fever, pancytopenia and hepatosplenomegaly and demonstrate characteristic splenic histopathological findings which include non-caseating granulomas in sarcoidosis and concentric perivascular laminations of fibrous tissue in small penicillar arteries resulting in the typical “onion skin” lesion of lupus spleen.

Another important observation in our study is the identification of an etiological diagnosis in approximately 40% (3/8) of patients with a non-diagnostic splenectomy, based on liver or lymph node specimens obtained during laparotomy. This observation highlights the importance of obtaining biopsy specimens from other intra-abdominal sites in addition to performing splenectomy during diagnostic laparotomy in PUO patients. In a study by Ozaras et al in 2005, the authors noted 17 diagnostic laparotomies for PUO were done over a 20-year period. Of these, a diagnosis was established in 13 patients with the most common diagnosis being tuberculosis (4 patients) and lymphoma in 6 patients (NHL in 3 patients, and HL in 3 patients). Laparotomy helped to exclude other causes in 2 patients diagnosed as Still’s disease. Overall, they reported a diagnostic rate of 88% in their study. Other studies report a laparotomy diagnostic rate ranging from 27% to 100%.

While none of the patients in our cohort suffered direct procedural complications, 10.5% died in the post-operative period. A majority of deaths appeared to be related to complications arising from the preceding systemic illness rather than from the procedure itself. In a 2017 study by Zhang et al, surgical complications occurred in 25.9% of patients and the 1-month operative mortality was 16.7%. Post-splenectomy complications may range from acute events such as intra-operative hollow viscus perforation, intra-abdominal hemorrhage, plural
effusions, pulmonary atelectasis and pancreatitis to long-term consequences that include overwhelming sepsis due to encapsulated organisms and enhanced atherosclerosis.

A few limitations merit mention. The small sample size of our cohort limits study generalizability. Also, the findings of our study may only be representative of those regions from where a majority of referrals were derived. The relatively short follow-up period of 6-weeks limits us from documenting the rate of sepsis due to encapsulated organisms, which is a well recognized long term complication in asplenic patients. The likelihood of this event occurring however would be low given the universal pre-surgical coverage with vaccines against encapsulated organisms in our cohort.

**Conclusions**

In conclusion, diagnostic laparotomy with splenectomy appears to have a high utility in evaluating PUO patients presenting with splenomegaly, especially when manifesting features of reticuloendothelial system involvement, in the setting of a negative extensive pre-surgical laboratory and radiological workup. The diagnosis of lymphoma appears more likely than an infectious cause in this subset of patients. Amongst infections, melioidosis is an important etiological differential to be considered in the Indian context.

**References**