骨髓檢查在不明熱的診斷價值及其預測因子
The diagnostic yield and predictive factors of bone marrow study in immunocompetent patients with fever of unknown origin

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Background: Bone marrow study (BMS) is increasingly used as a tool to search the cause of fever of unknown origin (FUO) in the medical centers of Taiwan now. As the etiologies of FUO usually vary across different countries, it is urgent to clarify the diagnostic yield and its predictive factors of this procedure.
Patients and methods: Between Jan 2006 and July 2013, there were 574 hematological consultations requested for 550 consecutive patients at the division of Infectious Diseases of Taipei Veterans General Hospital. Only patients who were sero-negative to human immunodeficiency virus and had received BMS to search the cause of FUO were enrolled. In addition, patients with nosocomial fever, history of hematological malignant diseases or who were immunocompromised were excluded. Immunodeficiency encompassed the following conditions: neutropenia (white blood cell counts <1000/μL and/or granulocyte counts < 500/μL, hypogammaglobulinemia (IgG < 50%), and solid organ transplant recipients. BMS should include bone marrow aspirate and biopsy, and/or accompanied culture or molecular analysis. The definition of FUO was set by Petersdorf and Beeson (Medicine (Baltimore). 1961;40:1-30.) included (1) duration of illness of more than 3 weeks before diagnosis and (2) repeatedly documented increased body temperature of more 38.3°C. Those who have received more than one BMS at last follow-up were analyzed only once for the first one (if all of the studies were non-diagnostic) or for the earlier one with the diagnostic finding. The data including clinical and laboratory parameters nearly at the time of BMS, the final diagnosis of FUO and survival status at last follow up was collected. The BMS is considered to have a diagnostic yield, if (1) the diagnosis of FUO was directly gained by the procedure, or (2) the findings of BMS provide important clues, which significantly contributed the final diagnosis of FUO. The overall survival (OS) was calculated from the date of bone marrow studies to last follow up. The comparisons of (1) all patients with vs. without the diagnostic yield of BMS, and (2) for the subgroup with the diagnostic yield of BMS, patients with hematological vs. non-hematological diseases were analyzed in terms of clinical and laboratory parameter, and OS. In addition, a logistic regression model was used to find the independent factor(s) relevant to the diagnostic yield of BMS and to the underlying hematological etiologies.
Results: 85 patients fulfilled the criteria, including 57 (67%) males and median age of 65 years (range, 19 to 94). BMA was done at a mean of 15 days (range 0-107) later after admission. 39 (46% of 85) patients had diagnostic yield of FUO, including hematological and non-hematological etiologies in 29 (74%) and 10 (26%) patients, respectively. The hematological etiologies included 15 (52% of 29) non-Hodgkin’s disease (B-cell immunophenotype [n=10]: diffuse large cell lymphoma [7], Burkitt’s lymphoma [2], intravascular B-cell lymphoma [1]; T cell [n=5]: peripheral T cell lymphoma [1], subcutaneous panniculitic T-cell lymphoma [1], nasal NK/T cell lymphoma [1]), angioimmunoblastic T-cell lymphoma [1]

and unclassified [1]), 2 Hodgkin's disease, 5 acute myeloid leukemia, 2 myeloproliferative neoplasms (myelofibrosis [1] and chronic myelomonocytic leukemia [1]), 1 myelodysplastic syndrome, 3 hemophagcytosis and 1 monoclonal gammopathy of undetermined significance. The non-hematological (n=10) included acid-fast stain positive granuloma in BM biopsy (1), positive PCR of Mycobacterium tuberculosis (TB) in BM (1), and only granuloma in the BM biopsy (8). For these 8 patients with granuloma in the BM biopsy only, TB and non-tuberculosis mycobacteria (NTM) were finally isolated from other tissues in 2 and 1 case, respectively. In addition, another one showed response to anti-TB treatment although no isolation of TB. For the remaining 49 with no diagnostic BMS, only 2 patients were finally to have hematological diseases, including Hodgkin's lymphoma (1) and splenic B-cell lymphoma (1) (P<0.001). Comparing to those without it, patients with a diagnostic yield of BMS had a higher proportion of leukopenia (P=0.025), neutropenia (P=0.019), thrombocytopenia (P<0.001) and an elevated serum level of lactate dehydrogenase (LDH) (P=0.029) and, furthermore, a lower OS (median 350 days vs. non-reached; P<0.001). The logistic regression model further found that thrombocytopenia (< 100,000/μL) (hazard ratio [HR]=4.1, 95% confidence interval [CI] 1.46–11.49, P=0.008) at the time of BMS was independently predictive to have a diagnostic yield. As for those with a diagnostic BMS, patients with hematological etiologies of FUO frequently had an elevated serum LDH (P=0.02), a trend of anemia (<10 g/dL; P=0.06), and a lower OS (hematological vs. non-hematological: median 46 days vs. 2569 days; P=0.006), compared to those with non-hematological etiologies. In the presence of a diagnostic BMS in FUO patients, anemia (<10 g/dL) was independently predictive to the underlying hematological etiologies (HR=8.7, 95% CI 1.3–58.8, P=0.013).

Conclusions: Using a cohort of patients in a tertiary medical center (with more than 2000 beds) of Taiwan, we found a relatively higher diagnostic yield (46%) of BMS in FUO patients. Thrombocytopenia (< 100,000/μL) at the time of BMS predicted its diagnostic yield. Comparing with those of Westerns countries, Taiwan FUO patients with a diagnostic BMS had a higher prevalence of T-cell non-Hodgkin's lymphoma and granuloma. The granuloma in the sections of BM biopsy was highly associated with underlying mycobacterial infections. In addition, FUO patients with a diagnostic BMS had a poor prognosis, especially for those with hematological etiologies.