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Original Article

A Comprehensive Analysis of 174 Febrile Patients Admitted to Okayama University Hospital

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Primary care physicians often encounter patients with fever of unknown origin and without apparent causes. Recent advances in laboratory medicine have facilitated diagnostic procedures; however, it is still difficult to determine the critical febrile factor at an early stage. We reviewed the medical records of 174 patients who were admitted due to a chief complaint of fever (> 37.5℃) to our hospital during the period from 2004 to 2010. The patients were categorized into patients with infection, inflammation, neoplasm and drug-induced fever. Based on the analysis done by category, it was revealed that the patient's age, body temperature and duration of fever were closely related to the final diagnosis. Serum CRP levels were significantly low in the nonbacterial infection group, while serum levels of sIL-2R were high in neoplasm and drug-induced cases. CRP level on admission was weakly but significantly correlated with body temperature, while duration of fever was inversely related to body temperature. The effectiveness of PET-CT and tissue biopsy for diagnosis was considerably high, particularly in the categories of neoplasm and nonspecific inflammation, respectively, though the effectiveness of bacterial culture was low. Thus, a careful review of physical and laboratory information including body temperature, CRP level, duration of fever, gender difference and history of medication is indispensable for diagnosis. Stepwise categorization and disease classification by comprehensive and systemic checkup are very helpful for determining the causes of fever.

Key words: computed tomography (CT), C-reactive protein (CRP), fluorodeoxyglucose positron emission tomography (FDG-PET), fever of unknown origin (FUO), soluble interleukin-2 receptor (sIL-2R)

Despite recent advances in diagnostic tools, fever of unknown origin (FUO) remains a crucial clinical problem [1–5]. Although general practitioners occasionally encounter patients with FUO, determining the cause of FUO remains a challenge in clinical practice. When further assessment is required in the diagnostic process, specialists in infectious diseases, rheumatologists, hematologists and endocrinologists are often consulted [6].

In 1961, Petersdorf and Beeson first provided the classical definition of FUO as a prolonged febrile illness of at least 3-week duration, with fever higher than 38.3℃ on several occasions, the cause of which is uncertain after 1 week of hospitalization and investigation [7]. In 1991, Durack and Street proposed 2 revisions of the definition [8]. The first change included classifications other than classical FUO, including nosocomial, neutropenic and HIV-associated

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FUOs. Secondly, the original restriction of the inpatient setting was modified to at least a 3-day hospitalization or 3 hospital visits for evaluating a febrile outpatient [8, 9].

For the diagnosis of FUO, an initial workup including complete and repeated history taking, physical examination, and obligatory investigations is an important process known as obtaining potentially diagnostic clues (PDCs) [5, 10]. PDCs are defined as all localizing signs, symptoms, and abnormalities potentially pointing to a diagnosis [11, 12]. Obtaining PDCs makes possible the differential diagnosis of a variety of possible causes of the fever. This process can also simplify further diagnostic procedures and limit a broad spectrum of possible diseases underlying FUO by ruling out less likely causes.

The currently used criteria for FUO were proposed more than 50 years ago. There have been many arguments that the criteria should be altered in accordance with changes in state-of-the-art medicine [1, 2, 13–16]. Since FUO is a very complicated category, there is no absolute algorithm that reliably leads to a final diagnosis or completely excludes particular diagnoses. General and/or primary care physicians must rely on very careful evaluation and detailed knowledge of a wide variety of diseases. The definition of FUO may also be carefully reconsidered depending on the patient's social, regional and medical background. In this regard, a recent report by Goto and colleagues may fit our current process for handling and diagnosing Japanese febrile patients [17]. They reported results of a retrospective study on hospitalized patients with fever in addition to classical FUO [17]. Based on their including a wide range of 226 febrile patients with axillar temperature >37℃, they concluded that strict use of the FUO definition is not always warranted when managing patients with prolonged fever.

Considering the background regarding FUO handling in Japanese medical institutes, we performed a systematic review of the medical records of 174 patients who were admitted due to persistent fever (>37.5℃) to our university hospital during a 7-year period from 2004 to 2010. Patients who did not completely match the classic criteria of FUO were also included in the present study. The patients were categorized into infection, inflammation, neoplasm and drug-induced fever groups. The clinical details of febrile patients in Okayama district were characterized in this study. An analysis of sub-classified categories revealed that initial clinical signs and conventional laboratory markers are very useful for achieving diagnosis in febrile patients at an early stage.

Subjects and Methods

Study subjects. We retrospectively reviewed the medical records of 174 febrile patients who were admitted to Okayama University Hospital during the period from Jan 2004 to Dec 2010 for the purpose of diagnosing the cause of a fever. Patients who were admitted due to a chief complaint of persistent fever, with an axillary temperature >37.5℃, were incorporated. The patients included 82 males (47%) and 92 females (53%), and the mean age on admission was 48.4 years (range: 15 to 92 years). Of the 174 patients, 146 (84%) had visited a city hospital and/or medical care clinic at least once. One hundred and twenty-seven (73%) of the patients were referred with documents and 44 (25%) of the patients were already hospitalized in the former medical institute(s). This protocol of the present study (No. 1496) was approved by the Institutional Review Board (IRB) of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

Laboratory examination and histological approach. White blood cell counts and serum C-reactive protein (CRP) levels were determined by an auto-analyzer system in the Central Laboratory of Okayama University Hospital. Serum CRP levels were determined by a latex-agglutination method using latex particles conjugated with anti-CRP antiserum, and the normal range was <0.3 mg/dl. Serum soluble interleukin-2 receptor (sIL-2R) levels were determined by an enzyme-linked immuno-sorbent assay using the IL-2R test − BML kit (BML, Tokyo), and the normal range was 122 to 496 U/ml. Tissue biopsies were performed for 55 febrile patients, and the regions of the biopsy included a total of 63 locations, including 30 biopsies in bone marrow, 19 in lymph nodes, 7 in skin/muscle, 3 in tumors, and 1 in a vessel and other symptom-related tissues such as the small intestine, spleen and kidney.

Scoring of the effectiveness of clinical examinations for diagnosis. Based on its clinical usefulness and contribution to the final diagnosis of FUO, each of the clinical examinations, including computed

tomography (CT) scan (plain and enhanced study), scintigraphy (including ^{67}Ga-scintigraphy), [^{18}F] fluorodeoxyglucose positron emission tomography (FDG/PET)-CT, biopsy, bacterial culture and QuantiFERON-TB test (QFT), was scored by at least three physicians in a daily clinical conference in our department as follows: not useful result = 0 points; useful result for differential diagnosis = 1 point; and directly diagnostic result = 2 points (full score). The percent effectiveness was calculated as the percentage of points obtained out of the total possible scores of individual examinations.

Statistical analysis. Results are shown as means ± SEM of the data. The data were subjected to ANOVA and a linear regression analysis to determine differences (StatView 5.0 software, Abacus Concepts, Inc., Berkeley, CA, USA). If differences were detected by ANOVA, Tukey–Kramer's post-hoc test was used to determine which means differed. P values < 0.05 were accepted as statistically significant.

Results

Categorization of the study population. As shown in Fig. 1A, the patients included in this study were categorized according to the diagnosis of the defined cause as follows: infection (41.4%), inflammation (27%), neoplasm (6.9%) and drug-induced fever (5.7%). For the remaining 33 cases (19%), no final diagnosis for FUO was determined, although the fever remitted spontaneously in all of those cases. The 5 categories were further classified into 7 subgroups including bacterial and non-bacterial infection, nonspecific inflammation, connective-tissue diseases, neoplasm, drug-induced and unidentified cases. The female/male ratio was high (> 60%) in the categories of connective-tissue diseases and nonspecific inflammation (Fig. 1B). On the other hand, the male/female ratio (> 60%) was high in drug-induced fever and unidentified fever.

Characterization of disease category. In the category of bacterial infection (Fig. 2A), the sources were classified by frequency as follows: urinary tract (17%) > cardiovascular system and abdominal cavity (10%) > respiratory system, head and neck, and sepsis (7%). Other sources included the prostate, lymph nodes, intestine and deep subcutaneous tissues. For non-bacterial infection (Fig. 2B), infections due to cytomegalovirus (CMV; 34%) and Epstein-Barr virus (EBV; 15%) were predominant, followed by infections due to viral meningitis (12%) and lymphadenitis (9%). Fungal infection was diagnosed in 2 cases (2.8% of the 72 infection-categorized cases). For the inflammation category, the major causes included connective-tissue diseases (21 cases) and nonspecific inflammation (26 cases). As shown in Fig. 3A, adult onset Still's disease (AOSD; 33%), polymyalgia rheumatica (PMR; 20%) and Behcet's disease

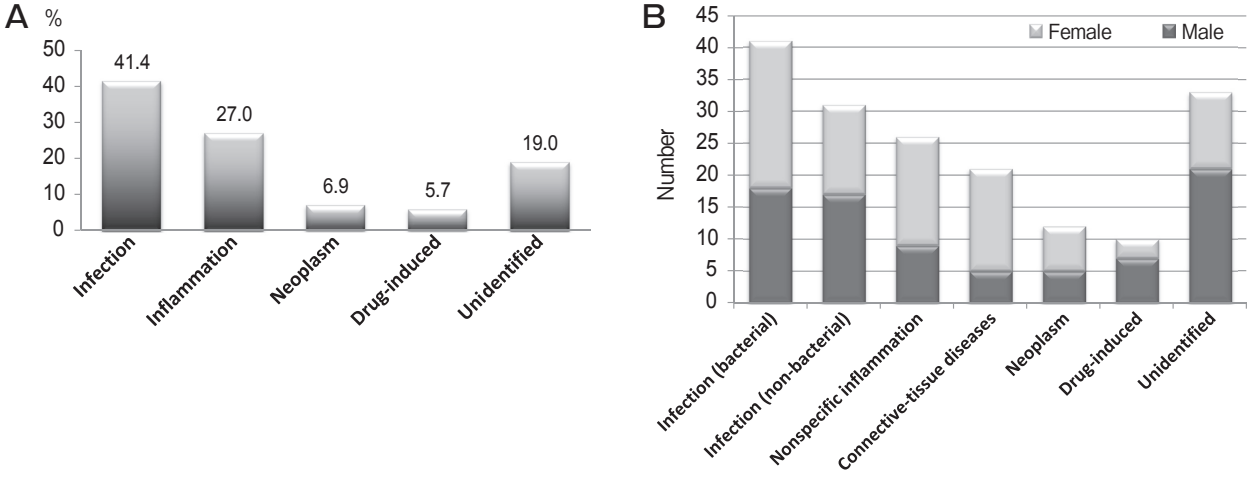

Fig. 1 Categorization of febrile patients. **A**, The 174 febrile patients were categorized into patients with infection (41.4%), inflammation (27%), neoplasm (6.9%), drug-induced fever (5.7%) and fever of unidentified cause (19%); **B**, These 5 categories were further classified into 7 subgroups including bacterial and non-bacterial infection cases, nonspecific inflammation and connective-tissue disease cases, neoplasm cases, drug-induced cases and unidentified cases. The female/male ratios are shown in the graphs.

(13%) were the major causes of fever, followed by polymyositis, remitting seronegative symmetrical synovitis with pitting edema (RS3PE; 7%) and systemic lupus erythematosus (SLE; 7%). As seen in Fig. 3B, nonspecific inflammation (26 cases) included many cases of necrotizing lymphadenitis (38%), and

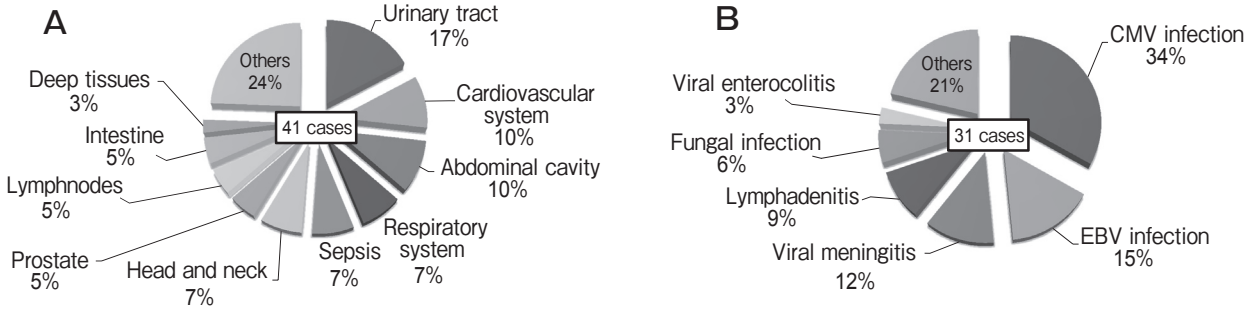

Fig. 2 Characterization of infection category. **A**, Breakdown of 41 bacterial infection cases with fever. The detected infection sources were as follows: urinary tract (17%) > cardiovascular system and abdominal cavity (10%) > respiratory system, head and neck, and sepsis (7%) > prostate, lymph nodes and intestine (5%) > deep tissues (3%); **B**, Breakdown of 31 non-bacterial infection cases with fever. CMV (34%) and EBV (15%) infection were predominant, being followed by viral meningitis (12%), lymphadenitis (9%) and viral enterocolitis (3%). Fungal infection occurred in only 2 cases (2.8% of the 72 infection-categorized cases).

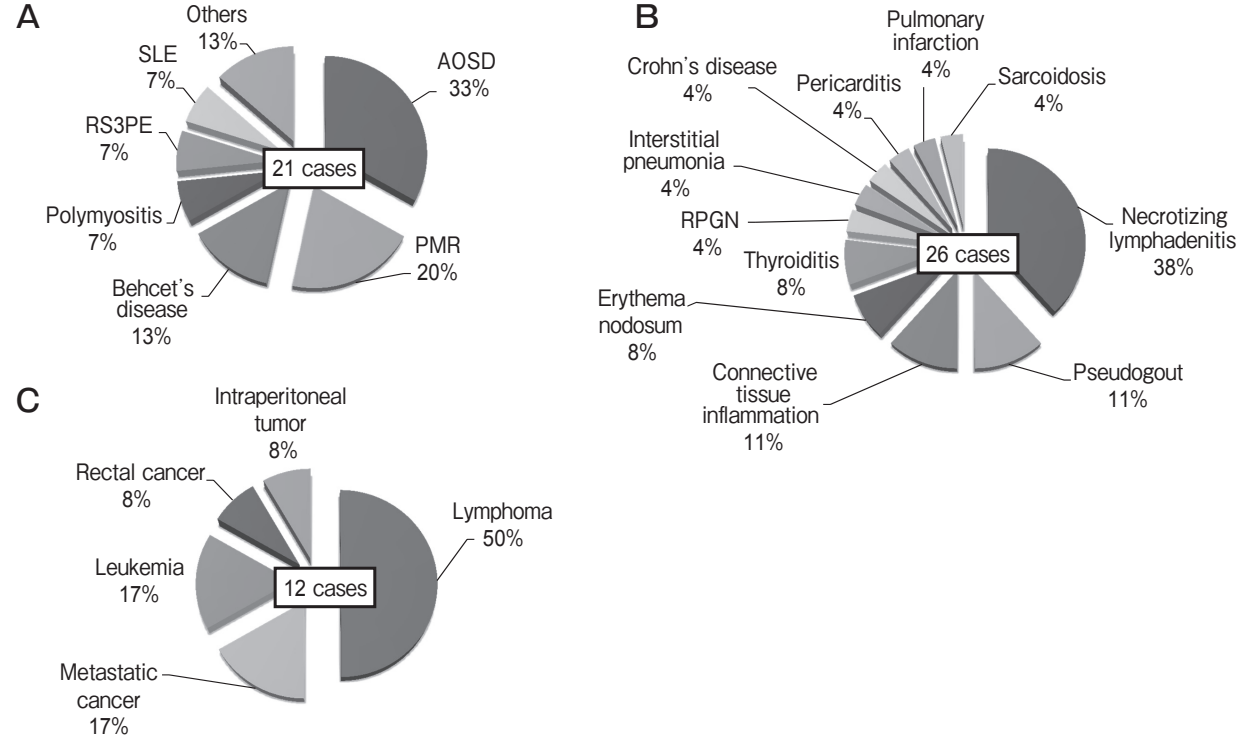

Fig. 3 Characterization of inflammation and neoplasm categories. **A**, Breakdown of 21 connective-tissue diseases with fever. AOSD (33%), PMR (20%) and, less frequently, Behcet's disease (13%) were the major causes of FUO, followed by polymyositis (7%), R3SPE (7%) and SLE (7%); **B**, Breakdown of 26 nonspecific inflammation cases with fever. This group included many cases of necrotizing lymphadenitis (38%), and the remaining cases were pseudogout (11%), connective tissue inflammation (11%), erythema nodosum (8%) and thyroiditis (8%). Other minor (4%) causes were RPGN, interstitial pneumonia, Crohn's disease, pericarditis, pulmonary infarction and sarcoidosis; **C**, Breakdown of 12 neoplasm cases with fever. This group predominantly included malignant lymphoma (50%), metastatic cancer (17%) and leukemia (17%) and, less frequently, rectal cancer (8%) and intra-peritoneal tumor (8%).

the remaining cases were pseudogout (11%), connective tissue inflammation (11%), and erythema nodosum and thyroiditis (8% each). Other minor (4%) causes were rapidly progressive glomerulonephritis (RPGN), interstitial pneumonia, Crohn's disease, pericarditis, pulmonary infarction and sarcoidosis. Fig. 3C shows the category of neoplasms (12 cases), including predominantly malignant lymphoma (50%), metastatic cancer (17%), leukemia (17%), rectal cancer (8%) and intraperitoneal tumor (8%).

Interrelationships between body temperature and clinical parameters. Correlations of body temperature with conventional parameters including WBC, serum levels of CRP and sIL-2R, and duration of fever were determined by linear regression analysis. As shown in Fig. 4, among the 4 parameters, CRP level on admission was weakly but significantly ($R^2 = 0.10$, $p < 0.01$) correlated with body temperature. Duration of fever was inversely related to body temperature ($R^2 = 0.06$, $p < 0.05$). The values of WBC and sIL-2R were not significantly related to the degree of the fever.

Clinical characteristics of sub-classified groups. Age, body temperature and duration of fever in the 7 subgroups were compared. As shown in Fig. 5, the average age of patients suffering nonbacterial infection was significantly younger (34.7 years old) than the average ages of patients in the other subgroups. It is notable that the degrees of fever in patients in the subgroups of nonbacterial infection, connective-tissue diseases and unidentified cases were significantly lower (< 38℃) than those in

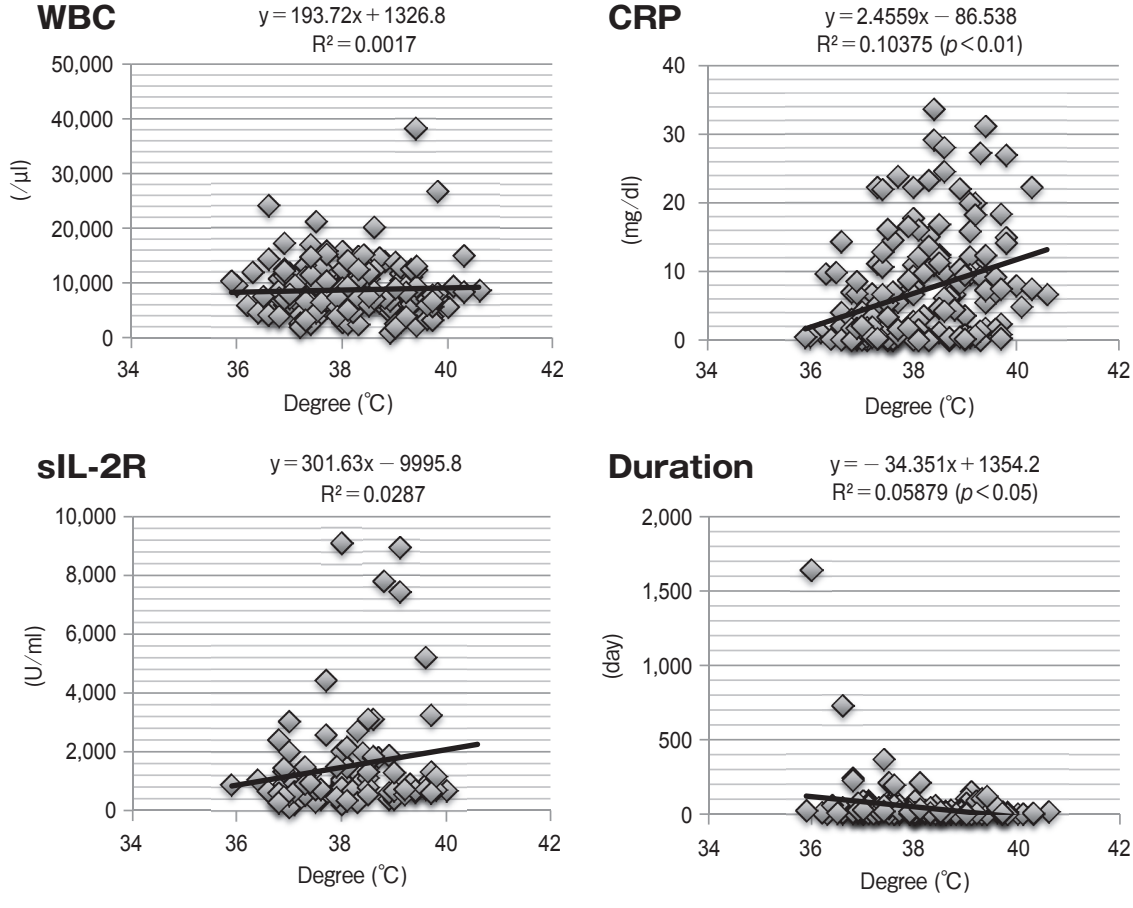

Fig. 4 Interrelationships of body temperature with clinical parameters. Correlations between body temperature and clinical parameters, including WBC, CRP and sIL-2R, and duration of fever were determined by linear regression analysis. Among the 4 parameters, CRP level on admission was weakly ($R^2 = 0.10$) but significantly ($p < 0.01$) correlated with body temperature. Duration of fever was inversely related to body temperature ($R^2 = 0.05$; $p < 0.01$).

patients in the other 4 subgroups (> 38℃). The durations of fever were longer in patients with connective-tissue diseases and neoplasms, lasting for almost 2 months (55–57 days). The unidentified cases also had a much longer duration of fever, lasting for more than 6 months (132 days).

Laboratory data of sub-classified groups. WBC, CRP and sIL-2R levels in the 7 subgroups were compared (Fig. 6). WBC levels were significantly lower (< 8,000/μl) in the subgroups of nonbacterial infection and nonspecific inflammation than in the other 5 groups. CRP levels were also significantly lower in the nonbacterial infection subgroup (< 1.5 mg/dl) and the subgroup of unidentified cases (< 4 mg/dl). The serum levels of sIL-2R were significantly higher in patients with neoplasms (> 3,000 U/ml) and, interestingly, in drug-induced cases (> 2,000 U/ml).

Effectiveness of clinical examinations for diagnosis. Clinical examinations included 150 CT scans (63 plain and 87 enhanced studies), 52 scintigraphy examinations (including 48 cases of ^{67}Ga-scintigraphy), 29 FDG/PET-CT scans, tissue biopsies of 63 specimens in 55 cases (biopsies from more than 1 tissue being performed in 8 patients), 130 bacterial cultures and 39 QFT assays (Fig. 7A). CT scans (86% of patients) and bacterial cultures (75%) were most frequently performed in the process of diagnosis. Among the 130 bacterial cultures, causal

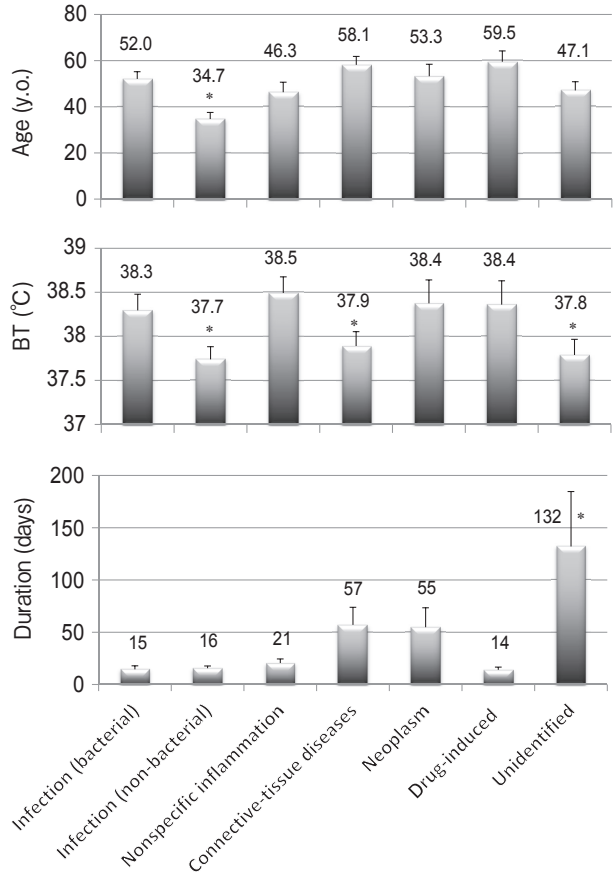

Fig. 5 Clinical differences among subclassified febrile groups. Among the 7 subgroups, patient's age (years), body temperature (℃) and duration of fever (days) were statistically analyzed. The results in each panel are shown as means ± SEM of data. The results were analyzed by ANOVA and, when a significant effect was observed, subsequent comparisons of group means were conducted. $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. control or between the indicated groups.

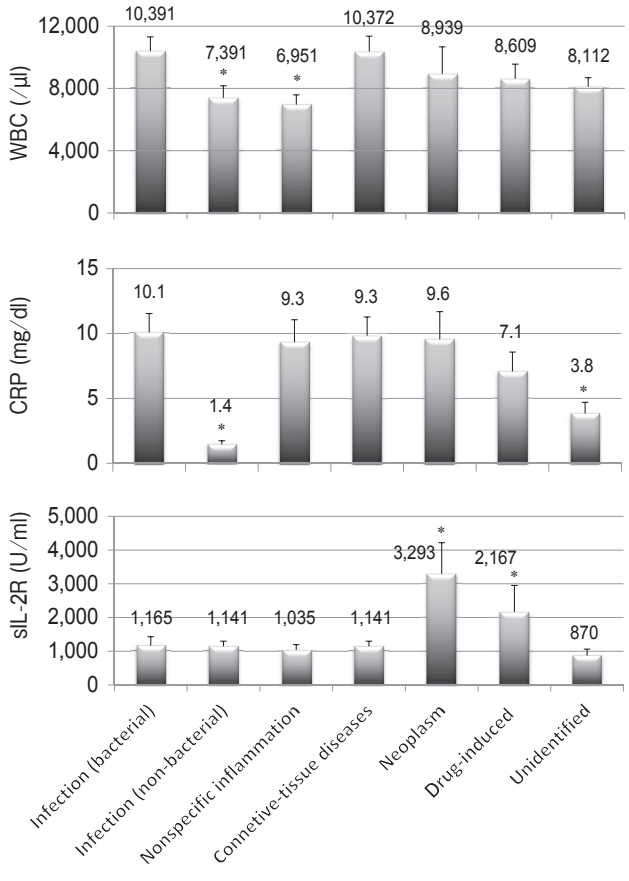

Fig. 6 Laboratory differences among subclassified febrile groups. Among the 7 subgroups, key laboratory data regarding WBC (/μl), CRP (mg/dl) and sIL-2R (U/ml) levels were statistically analyzed. The results in each panel are shown as means ± SEM of data. The results were analyzed by ANOVA and, when a significant effect was observed, subsequent comparisons of group means were conducted. $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. control or between the indicated groups.

bacteria were positively detected in 16 cases (12%) (Fig. 7B). The causal bacteria included *E. coli* (25%), *Streptococcus* (25%), *Staphylococcus* (19%) and *Campylobacter* (7%). The sample sources were predominantly from blood cultures (65%) and urine (17%) and less often from pus (12%) and cerebrospinal fluid (CSF; 6%). As shown in Fig. 7C, %effectiveness as determined by CT scan (plain as well as enhanced study) and scintigraphy was found to be approximately ~30%, whereas that determined by PET-CT (51.7%) and that determined by biopsy (63.6%) were found to be considerably higher. In contrast, the effectiveness of bacterial culture was unexpectedly low (12.3% in all cases and 28.1% in infection-category cases). The effectiveness of QFT for the diagnosis of the febrile cause was relatively low (15.4%).

Scoring of effectiveness by PET-CT and biopsy for diagnosis. The cases that underwent PET-CT and biopsies are shown in Fig. 8. PET-CT examination was performed when connective-tissue disease and neoplasm were clinically suspected for the etiology of the fever, and PET-CT was the most effective method for the detection of neoplasms (Fig. 8A). Tissue biopsies were often performed for diagnosis and/or to rule out the categories of nonspecific inflammation, neoplasm, unidentified cases and connective-tissue diseases (Fig. 8A). For the diagnosis of the infection category, PET-CT and biopsy studies were the least often carried out. As shown in Fig. 8B, biopsy studies for bone marrow (30 cases), lymph nodes (19 cases) and skin/muscle (7 cases) were the most-often performed, with lymph-node biopsies being applicable to the diagnosis of the category of nonspecific inflammation and with bone marrow and tumor specimens being informative for determining the existence of a neoplasm.

Discussion

In the present study, we reviewed the medical records of 174 patients who were admitted to our hospital due to persistent fever (> 37.5℃) during a 7-year period. The patients were categorized into 5 groups including infection, inflammation, neoplasm, drug-induced fever and unidentified fever groups (Fig. 9). Further classification into 7 groups revealed physical and laboratory characteristics depending on

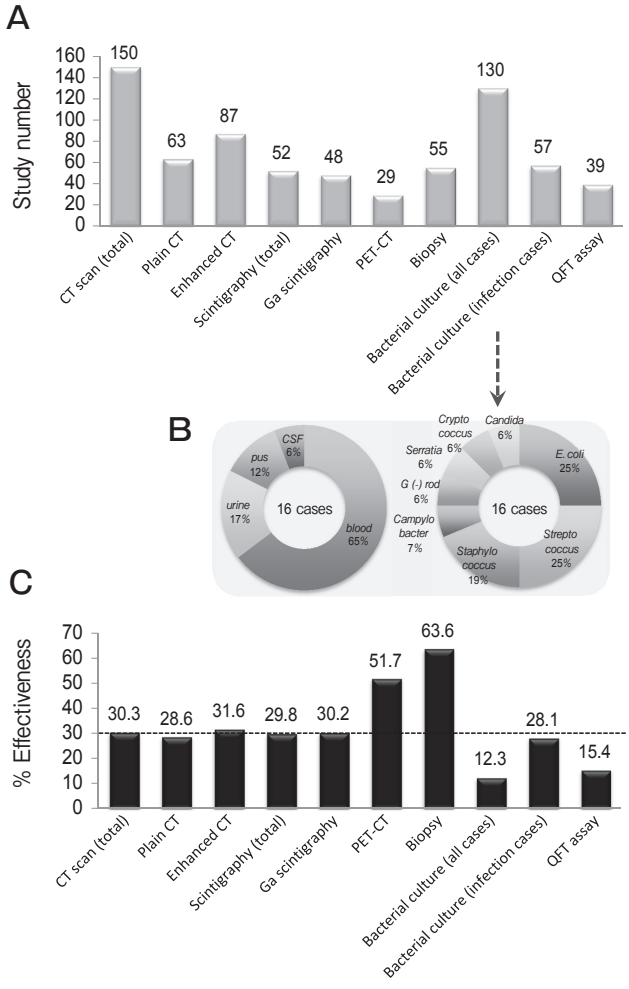

Fig. 7 Effectiveness of clinical examinations for the diagnosis of the cause of a fever. **A**, Clinical examinations performed in the present study included 150 CT scans (63 plain and 87 enhanced studies), 52 scintigraphy examinations (including 48 cases of ^{67}Ga-scintigraphy), 29 FDG/PET-CT scans, 55 biopsy cases, 130 bacterial cultures (57 cases included in the infection category) and 39 QFT examinations; **B**, Breakdown of detected bacteria: Out of 130 bacterial cultures, causal bacteria including *E. coli*, Streptococcus, Staphylococcus and Campylobacter were detected in 16 cases. The samples were from blood and urine samples and, less often, from pus and CSF; **C**, Evaluation of the effectiveness of examinations by "effective scoring". Based on the relative usefulness and contribution to the final diagnosis of fever, effective scoring was utilized. The effectiveness was ~30% (shown by a dotted line) for CT scan (total, plain and enhanced), scintigraphy (total), ^{67}Ga-scintigraphy and bacterial culture (of infection cases), which was lower than the effectiveness of 50% for PET-CT and biopsy, and higher than the effectiveness of 20% for bacterial culture (of all cases) and QFT.

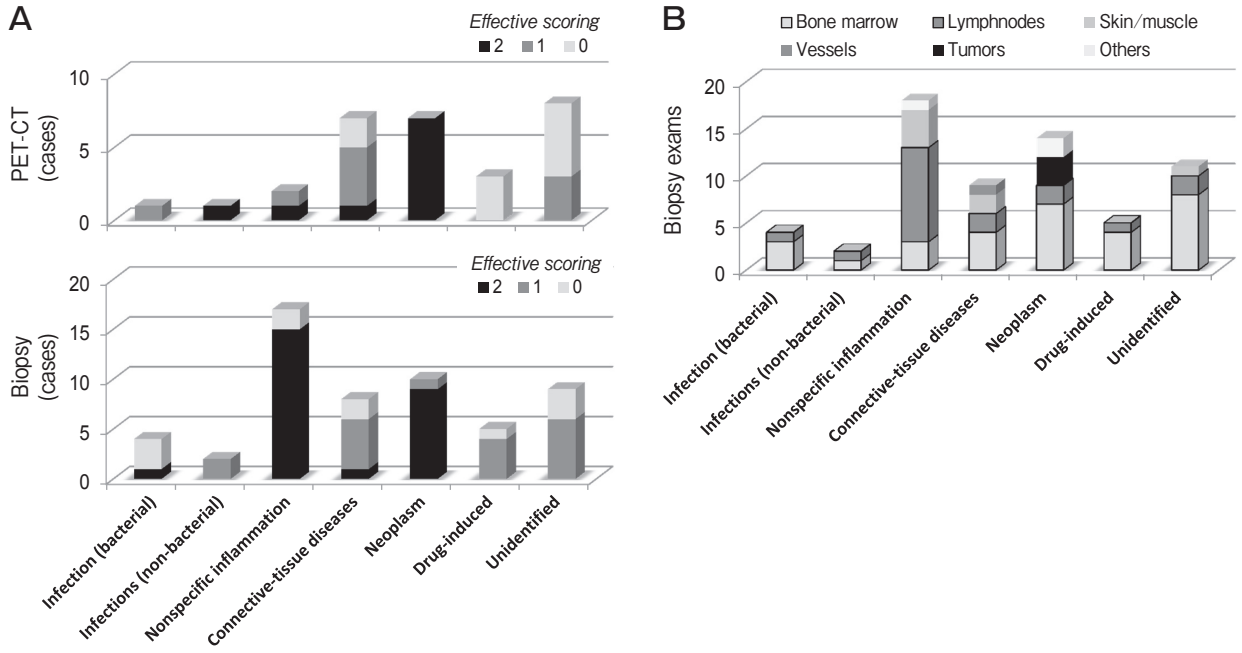

Fig. 8 Details of PET-CT and biopsy for diagnosis of febrile cause. **A**, Effective scoring of PET-CT and tissue biopsies in each category. FDG/PET-CT scans in 29 cases and 63 tissue biopsies in 55 cases were performed. The numbers of patients with effective scoring (0 to 2 points) in the 7 febrile categories are shown in each graph; **B**, Study number of tissue biopsies in each category: 63 tissue biopsies in 55 cases were performed. The numbers of examined tissues including bone marrow, lymph nodes, skin/muscle, vessels, tumors and others are shown on the basis of the 7 febrile categories.

the causes of fever.

The 5 major categories of febrile causes were established according to previous reports [7, 11–14, 18, 19]. In comparison with our data, the percentages of the 3 major categories of FUO, infection (41% in the present study vs. 25–36% in the literature), tumor (6.9% vs. 7–31%) and collagen vascular and granulomatous diseases (27% vs. 17–26%), remained almost unchanged throughout several FUO studies performed in different periods [20]. Iikuni *et al.* analyzed the causes of FUO in 153 Japanese patients in a university hospital from 1982 to 1992 [21] and found that infection and neoplasm were the most frequent causes of fever. According to a study of 80 FUO patients in the Shinetsu area in 1986–1992 by Shoji *et al.* [22], the number of neoplasm-induced FUO cases decreased, while the number of FUO cases related to connective-tissue diseases such as AOSD increased. These trends were similar to those in our study, resulting in a relatively low rate of malignancy (6.9% of total cases) and high frequencies of AOSD and PMR (33% and 20% of connective-tissue diseases, respectively).

Recent developments in radiological techniques such as FDG-PET has greatly improved the ability to diagnose occult malignancies and origins of inflammation [10, 23]. Increased uptake and retention of FDG are shown in lesions with a high concentration of granulocytes and activated macrophages in acute and chronic inflammation [24]. The diagnostic usefulness of FDG-PET for patients with FUO was reported to be 36% [25]. We have been utilizing FDG-PET for febrile patients since 2007, with a diagnosis being made in 9 of 28 febrile patients who underwent FDG-PET. FDG-PET was more useful (51.7% of patients) than ^{67}Ga-scintigraphy (31.2%) for diagnosing malignant lymphoma and metastatic cancers as causes of fever. However, we cannot exclude the possibility of selection bias in the diagnosis of the cause of fever using PET-CT.

After the localization of a febrile source, biopsy is often required to pathologically diagnose its inflammatory or neoplastic origin. In the present series of 55 biopsies, biopsy examination was diagnostically useful in 44 cases, resulting in a 63.6% rate of effectiveness, which was higher than that of FDG-PET

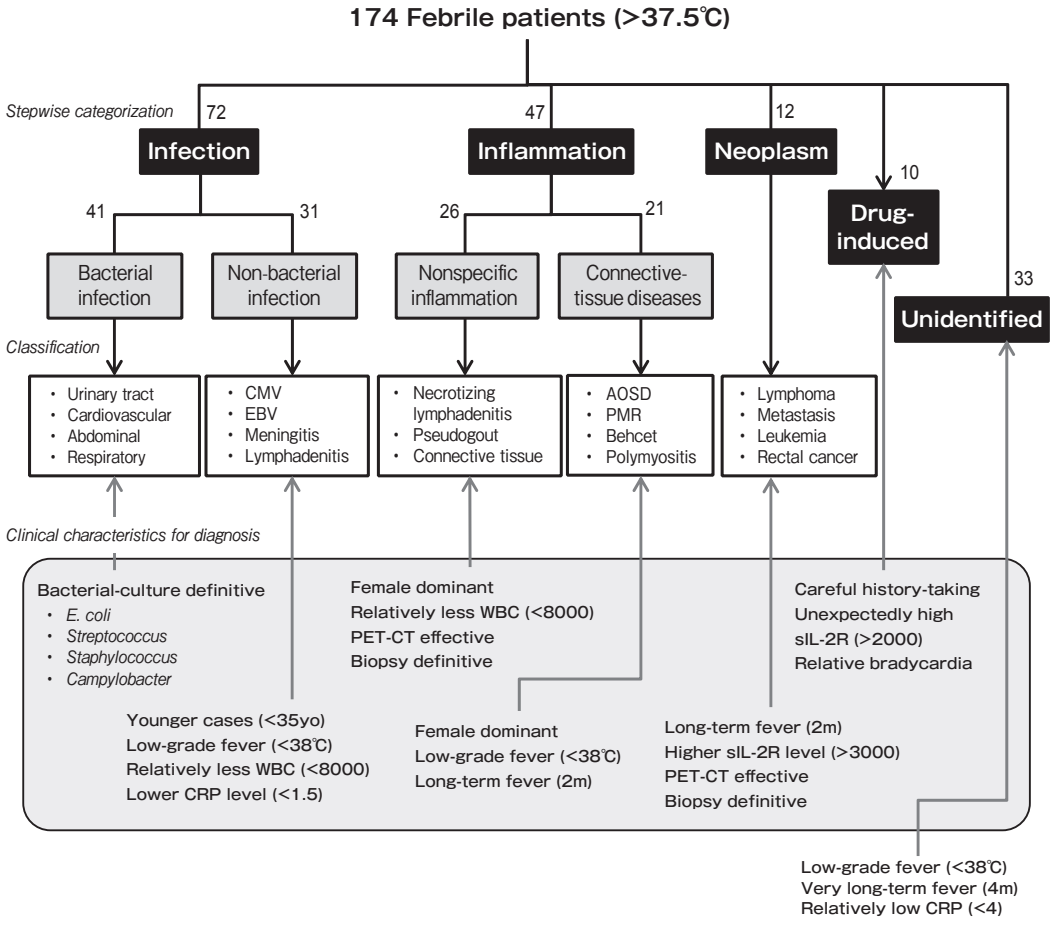

Fig. 9 Categorization and clinical characteristics of febrile diseases. Stepwise categorization of febrile diseases is useful for differentiating various febrile disorders. Body temperature, CRP levels, duration of fever and gender differences provide useful information for the initial narrowing of the list of possible causes of fever. FDG-PET and biopsy study are particularly effective for the diagnosis of neoplasm, nonspecific inflammation and connective-tissue diseases. At the same time, assessing infection etiology by bacterial culture and the exclusion of drug-induced fever are also important.

(51.7%). The pathology of biopsy specimens from bone marrow, lymph nodes and skin/muscle was crucial for the diagnosis of fever. Lymph node specimens were useful for the category of nonspecific inflammation, and bone marrow and tumor specimens were diagnostic for neoplasms. Thus, biopsy was found to be very effective for determining febrile diseases after an adequate search for the localization. When infection etiology is excluded from the causes of fever, combined PET-CT and biopsy examinations may effectively cover 3 febrile categories including nonspecific inflammation, connective-tissue disease and neoplasm.

Regarding the miscellaneous causes of FUO, the possibility of drug-induced fever should always be considered [26]. Drug-induced fever occurs in 3–5% of hospitalized patients with variable patterns of onset and duration [27]. In the present series, 10 febrile patients, including 8 patients referred from other specialists, were found to have drug-induced fever. Six of the 10 patients with drug-induced fever in our study showed slight bradycardia, which is known to be a characteristic of drug-induced fever [26]. The causal agents included antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), general cold medicine and Chinese medicine. Four cases were detected by a drug-induced lymphocyte stimulation test (DLST). In our cases of drug-induced fever, the fever disappeared in 3 to 24 days after cessation of the administration of the causal drugs. It was of interest that the body

temperature was unexpectedly high (>38℃) on admission in 6 of those 10 patients.

Serum sIL-2R levels have been shown to be high in patients with neoplastic, autoimmune, or inflammatory diseases [28] and to correlate with the extent of histologic malignancy and clinical aggressiveness of non-Hodgkin's lymphomas [29]. In the present study, patients with fever due to malignant lymphomas showed high serum levels of sIL-2R (>3,000 U/ml). It was also notable that patients with drug-induced fever also showed increased levels of serum sIL-2R, though the levels were much lower (~2,000 U/ml) and fluctuated compared with neoplastic cases. Kluge *et al.* reported a number of interesting cases in which a fever was induced by the antipsychotic drug clozapine [30]. Serum sIL-2R levels were found to be high in clozapine-treated febrile patients with the activation of cytokines and the receptors induced by the drug.

As for other laboratory tests in our study, QFT data were partially informative for the diagnosis of fever. In our series, 6 cases were positive out of the 39 examined cases, and only 1 case was finally diagnosed as tuberculosis-induced fever. Although the effectiveness of QFT screening was unexpectedly low (15% of the patients), it is important as a way to eliminate the possibility of occult tuberculosis in elderly patients and in immunodefective patients [31]. Serum anti-HIV examination was performed in 43 febrile cases after individual permission was given, with no positive case being found. Screening for anti-HIV antibody and/or determination of the CD4/8 ratio are required at an early stage to exclude HIV-associated fever [32], although regional and social differences may exist in Japan. Also, we could not include data for procalcitonin (PCT) because of an insufficient number of cases. Plasma concentrations of PCT have been shown to increase more rapidly than CRP in patients with bacterial and fungal infections, whereas, in contrast to CRP, PCT is not elevated in patients with inflammation of a noninfectious origin [33]. We would like to obtain new information regarding FUO diagnosis using PCT screening in a future study.

The causes of FUO differ depending on the patient's age [34–36]. Self-limited viral infections with high fever are uncommon as causes in elderly patients, while temporal arteritis, tumors and tuberculosis are more likely in elderly patients [34]. Connective-tissue diseases such as temporal arteritis, rheumatoid arthritis (RA) and PMR cause about 25% of FUO cases in elderly patients, and malignancy accounts for 10–20% of FUO cases [37, 38]. Therefore, FUO in elderly patients should be defined as a low-grade fever, such as a persistent oral or tympanic membrane temperature >37.2℃, persistent rectal temperature >37.5℃, or an increase over the baseline temperature of >1.3℃ [34]. In this regard, Goto and colleagues reported the results of a retrospective study on hospitalized patients with fever in addition to classical FUO [17]. Their study included a wide range of 226 prolonged-febrile patients with an axillar temperature >37℃. They noted that there was a considerable number of patients with critical diseases including intra-abdominal abscess, sarcoidosis, ulcerative colitis, Castleman's disease, malignancies and panhypopituitarism even among patients who had prolonged fever but did not completely meet the FUO definition [17]. In the present study, we carefully examined patients with a body temperature >37.5℃ and then diagnosed the causes of the fever. However, a bias due to the physician who first treated the patient might exist [3, 39]. In addition, there were still 33 patients (19%) with fevers of unidentified origin, although the fever slowly normalized spontaneously in these cases. These cases of fever might have included cases of factitious fever, allergic fever or self-limiting inflammation. Although FUO patients who remain undiagnosed after extensive evaluation generally have favorable outcomes [3], careful follow-up to rule out malignancy, recurrent inflammation or occult connective-tissue disease is needed.

Collectively, the results of the present study suggested that the categorization of febrile diseases is a very useful process for differentiating the original disorders (Fig. 9, *from the top*). Among clinical parameters, body temperature, CRP levels, duration of fever and gender differences provide important information to narrow down the list of causes of a fever (Fig. 9, *from the bottom*). The exclusion of drug-induced fever is also necessary. FDG-PET and biopsy are effective for the diagnosis of neoplasm and nonspecific inflammation, whereas bacterial culture might include false-negative results due to therapeutic bias. Stepwise categorization by means of comprehensive and systemic checkup is necessary for general physicians in order to diagnose FUO at an early stage.

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References

1. Jacoby GA and Swartz MN: Fever of undetermined origin. N Engl J Med (1973) 289: 1407–1410.
2. Esposito AL and Gleckman RA: A diagnostic approach to the adult with fever of unknown origin. Arch Intern Med (1979) 139: 575–579.
3. Arnow PM and Flaherty JP: Fever of unknown origin. Lancet (1997) 350: 575–580.
4. Cunha BA: Fever of unknown origin. Infect Dis Clin North Am (1996) 10: 111–127.
5. Gaeta GB, Fusco FM and Nardiello S: Fever of unknown origin: A systematic review of the literature for 1995–2004. Nucl Med Commun (2006) 27: 205–211.
6. Varghese GM, Trowbridge P and Doherty T: Investigating and managing pyrexia of unknown origin in adults. BMJ (2010) 341: C5470.
7. Petersdorf RG and Beeson PB: Fever of unexplained origin: Report on 100 cases. Medicine (Baltimore) (1961) 40: 1–30.
8. Durack DT and Street AC: Fever of unknown origin--reexamined and redefined. Curr Clin Top Infect Dis (1991) 11: 35–51.
9. Roth AR and Basello GM: Approach to the adult patient with fever of unknown origin. Am Fam Physician (2003) 68: 2223–2228.
10. Bleeker-Rovers CP, van der Meer JW and Oyen WJ: Fever of unknown origin. Semin Nucl Med (2009) 39: 81–87.
11. de Kleijn EM, van Lier HJ and van der Meer JW: Fever of unknown origin (fuo). Ii. Diagnostic procedures in a prospective multicenter study of 167 patients. The netherlands fuo study group. Medicine (Baltimore) (1997) 76: 401–414.
12. de Kleijn EM, Vandenbroucke JP and van der Meer JW: Fever of unknown origin (fuo). I a. Prospective multicenter study of 167 patients with fuo, using fixed epidemiologic entry criteria. The netherlands fuo study group. Medicine (Baltimore) (1997) 76: 392–400.
13. Knockaert DC, Vanneste LJ, Vanneste SB and Bobbaers HJ: Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. Arch Intern Med (1992) 152: 51–55.
14. Larson EB, Featherstone HJ and Petersdorf RG: Fever of undetermined origin: Diagnosis and follow-up of 105 cases, 1970–1980. Medicine (Baltimore) (1982) 61: 269–292.
15. Petersdorf RG: Fever of unknown origin. An old friend revisited. Arch Intern Med (1992) 152: 21–22.
16. Kashiwagi H: Fever of unknown origin: A changing diagnostic spectrum. Intern Med (1994) 33: 65–66.
17. Goto M, Koyama H, Takahashi O and Fukui T: A retrospective review of 226 hospitalized patients with fever. Intern Med (2007) 46: 17–22.
18. Knockaert DC, Vanneste LJ and Bobbaers HJ: Recurrent or episodic fever of unknown origin. Review of 45 cases and survey of the literature. Medicine (Baltimore) (1993) 72: 184–196.
19. Kazanjian PH: Fever of unknown origin: Review of 86 patients treated in community hospitals. Clin Infect Dis (1992) 15: 968–973.
20. Amin K and Kauffman CA: Fever of unknown origin. A strategic approach to this diagnostic dilemma. Postgrad Med (2003) 114: 69–75.
21. Iikuni Y, Okada J, Kondo H and Kashiwazaki S: Current fever of unknown origin 1982–1992. Intern Med (1994) 33: 67–73.
22. Shoji S, Imamura A, Imai Y, Igarashi A, Yazawa M, Hirahara K, Kagoshima M, Ono M, Nakajima K and Iguchi K: Fever of unknown origin: A review of 80 patients from the shin'etsu area of japan from 1986–1992. Intern Med (1994) 33: 74–76.
23. Meller J, Sahlmann CO, Gurocak O, Liersch T and Meller B: Fdg-pet in patients with fever of unknown origin: The importance of diagnosing large vessel vasculitis. Q J Nucl Med Mol Imaging (2009) 53: 51–63.
24. Gotthardt M, Bleeker-Rovers CP, Boerman OC and Oyen WJ: Imaging of inflammation by pet, conventional scintigraphy, and other imaging techniques. J Nucl Med (2010) 51: 1937–1949.
25. Jaruskova M and Belohlavek O: Role of fdg-pet and pet/ct in the diagnosis of prolonged febrile states. Eur J Nucl Med Mol Imaging (2006) 33: 913–918.
26. Woolery WA and Franco FR: Fever of unknown origin: Keys to determining the etiology in older patients. Geriatrics (2004) 59: 41–45.
27. Lipsky BA and Hirschmann JV: Drug fever. Jama (1981) 245: 851–854.
28. Zerler B: The soluble interleukin-2 receptor as a marker for human neoplasia and immune status. Cancer Cells (1991) 3: 471–479.
29. Olejniczak K and Kasprzak A: Biological properties of interleukin 2 and its role in pathogenesis of selected diseases--a review. Med Sci Monit (2008) 14: RA179–189.
30. Kluge M, Schuld A, Schacht A, Himmerich H, Dalal MA, Wehmeier PM, Hinze-Selch D, Kraus T, Dittmann RW and Pollmacher T: Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever. Psychoneuroendocrinology (2009) 34: 118–128.
31. Simpson T, Fox J, Crouse K and Field K: Quantitative and qualitative quantiferon((r))-tb gold in-tube results among groups with varying risks of exposure to tuberculosis. Heart Lung (2012) 41: 553–561.
32. Hot A, Schmulewitz L, Viard JP and Lortholary O: Fever of unknown origin in hiv/aids patients. Infect Dis Clin North Am (2007) 21: 1013–1032, ix.
33. Schuttrumpf S, Binder L, Hagemann T, Berkovic D, Trumper L and Binder C: Procalcitonin: A useful discriminator between febrile conditions of different origin in hemato-oncological patients? Ann Hematol (2003) 82: 98–103.
34. Norman DC: Fever in the elderly. Clin Infect Dis (2000) 31: 148–151.
35. Tal S, Guller V and Gurevich A: Fever of unknown origin in older adults. Clin Geriatr Med (2007) 23: 649–668, viii.
36. Tal S, Guller V, Gurevich A and Levi S: Fever of unknown origin in the elderly. J Intern Med (2002) 252: 295–304.
37. Knockaert DC, Vanneste LJ and Bobbaers HJ: Fever of unknown origin in elderly patients. J Am Geriatr Soc (1993) 41: 1187–1192.
38. Matsumoto Y, Sada KE, Takano M, Toyota N, Yamanaka R, Sugiyama K, Wakabayashi H, Kawabata T, Otsuka F and Makino H: Risk factors for infection in patients with remitted rheumatic diseases treated with glucocorticoids. Acta Med Okayama (2011) 65: 329–334.
39. Williams J and Bellamy R: Fever of unknown origin. Clin Med (2008) 8: 526–530.