Analysis of 256 cases of classic fever of unknown origin

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Abstract

Objective: Causes of fever of unknown origin (FUO) vary depending on region and time period. The present study of patients with classic FUO investigated differences based on patient background factors such as age and causative diseases, and changes that have occurred over time.

Methods: We extracted and analyzed data from the medical records of 256 patients ≥18 years old who met the criteria for classic FUO and were hospitalized between August 1, 1994 and December 31, 2012.

Results: Median age of patients was 55 years (range, 18-94 years). The cause of FUO was infection in 27.7% of patients (n=71), non-infectious inflammatory disease (NIID) in 18.4% (47), malignancy in 10.2% (26), other in 14.8% (38), and unknown in 28.9% (74). The most common single cause was HIV/AIDS in 17 patients. NIID and malignancy were more common in patients ≥65 years old than in patients <65 years old. During 2004-2012, compared to 1994-2003, infections and “other” causes were decreased, whereas NIID, malignancy, and unknown causes were increased.

Conclusion: FUO associated with HIV/AIDS is increasing in Japan. In addition, as in previous studies in Japan and overseas, our study showed that the number of patients in whom the cause of FUO remains unknown is increasing and exceeds 20% of cases. The present study identified diseases that should be considered in the differential diagnosis of FUO, providing useful information for the future diagnosis and treatment of FUO.

Key words: HIV/AIDS, malignant lymphoma, image studies

Background

Fever of unknown origin (FUO) was defined by Petersdorf and Beeson in 1961 as a fever of ≥38.3°C that lasts for ≥3 weeks and remains undiagnosed even after 1 week of inpatient evaluation (1). In 1991, Durack and Street further classified FUO into classic FUO, nosocomial FUO, neutropenic FUO, and human immunodeficiency virus (HIV)-associated FUO. In addition, “undiagnosed after 1 week of inpatient evaluation” has been changed to “undiagnosed after 3 outpatient visits or 3 days of inpatient evaluation,” so the criteria are now also applicable to outpatients (2).

FUO can be caused by many diseases that vary depending on region and time period. The causes of FUO are generally considered to be infection, non-infectious inflammatory disease (NIID), and malignancy (1-9). In the existing literature, causes of FUO have been classified into 5 categories: infection, NIID, malignancy, other, and unknown (5,8-17). Studies on the causes of FUO have occasionally been reported in Japan, but the number of cases has been small, often representing regional studies limited to a single hospital (13-17). The first nationwide retrospective study of FUO in Japan has recently been reported (18). Pediatric case studies of FUO in Japan have also been collectively reported (19). However, accumulating cases of hospitalized patients meeting the criteria for classic FUO is not easy. Unless a hospital is mid-sized or larger and receives referrals from other hospitals for further testing, or unless there is collaboration with other institutions, acquiring a sufficient number of cases is difficult. Over the subsequent approximately 10-year period, numbers of FUO patients referred for further testing or admitted to our hospital have increased (20). The aim of the present study was thus to investigate recent trends in classic FUO; specifically, differences based on patient background factors such as age and causative diseases, and

changes that have occurred over time.

Methods

For the present single-institution retrospective observational study at a 1020-bed university-affiliated hospital in Tokyo, data were extracted from the medical records of patients ≥18 years old who met the criteria for classic FUO and were hospitalized between August 1, 1994, when our department was established, and December 31, 2012. Patients treated in the hospital are referred from a wide geographic distribution throughout Japan (75.4% from Tokyo, 22.1% from Eastern Japan other than Tokyo, and 2.7% from Western Japan; N=32,149, data as of 2012). The criteria of Durack and Street for classic FUO were used in this study: fever ≥38°C at least twice over a ≥3-week period, lack of a diagnosis after 3 outpatient visits or 3 days of hospitalization, and no diagnosis of HIV or immunodeficiency prior to the fever (2). Temperatures were measured as axillary temperature, which is often measured in Japan.

Causes of FUO were classified as infection, NIID, malignancy, other, and unknown, based on medical records by the physician in charge of each patient. All cases in which causes were only suspected, not confirmed, were classified as unknown. Because categorizations of specific diseases sometimes differ between studies, previous articles were used as references for the present study (5,9,21).

The following data were compiled and analyzed in the present study.

<1> Age group, sex, and causes of FUO (%) in all patients.

<2> Differences in causes of FUO (%) between patients ≥65 years old and <65 years old.

<3> Differences in causes of FUO (%) between the periods 1994-2003 and 2004-2012.

<4> Number of cases requiring ≥150 days from the time of fever onset for diagnosis.

Results

A total of 256 patients were enrolled in this study, including 131 men and 125 women, with a median age of 55 years (range, 18-94 years). The most frequent age group comprised patients in their 60s (Fig. 1). Patients ≥65 years old accounted for 33.2% (85/256) of all patients. The cause of FUO was infection in 27.7% of patients (n=71), NIID in 18.4% (n=47), malignancy in 10.2% (n=26), other in 14.8% (n=38), and unknown in 28.9% (n=74). The most common single cause was HIV/acquired immunodeficiency syndrome (AIDS) in 17 patients, accounting for 25% of all infections. Among these, 16 patients were <65 years old. The next leading causes were malignant lymphoma and infective endocarditis in 12 patients each; with these causes, 4 patients and 10 patients, respectively, were <65 years old. The fourth leading cause was polymyalgia rheumatica in 10 patients; 7 were ≥65 years old (Table 1).

In patients ≥65 years old, compared to those <65 years old, percentages of infections (21.7% vs. 30.6%) and other causes (7.2% vs. 18.5%) were lower, whereas percentages of NIID (27.7% vs. 13.9%) and malignancy (14.5% vs. 8.1%) were higher. The percentage of unknown causes was the same (28.9%) in both patients <65 years old and ≥65 years old (Table 2). In 2004-2012, compared to 1994-2003, the percentages of NIID, malignancy, and unknown causes tended to increase (Fig. 2). Among cases with a diagnosed cause, ≥150 days from fever onset were required for diagnosis in 8 patients. The longest time to diagnosis was 325 days in a case of adult Still's disease (Table 3).

Discussion

The causes of classic FUO vary with region and time period. In reports before the 1990s, infections were the leading cause, whereas NIID and unknown causes have increased more recently (5,9). Data from the 1950s to the early 1990s have been compiled, and unknown causes have accounted for ≥20% of cases since the 1990s (22,23). Our study also found a high percentage (28.9%) of unknown causes of FUO. One reason for this increase in unknown causes may be as follows. In a university hospital like ours, many patients who are referred from other hospitals for further evaluation of FUO have already undergone routine tests by their local physician because of the wider availability of testing. The ratio of patients with FUO referred from other hospitals gradually increased from 59.6% in 1994-2003 to 68.2% in 2004-2012. There are therefore more cases where a diagnosis cannot be reached despite repeated testing.

Trends for some high-frequency cases are similar to findings from previous reports, but the increase in HIV/AIDS is noteworthy. The number of HIV/AIDS patients in Japan is increasing. In 2012, there were 1,002 new cases of HIV infection and 447 patients with AIDS reported. Before 2012, a total of 14,706 cases of HIV infection and 6,719 AIDS patients had been reported. The number of newly infected persons increased from 1985 to 2008. Although there has been no subsequent increase, there has also not been any clear decrease (24). The number of these patients is expected to continue to increase in Japan, so HIV/AIDS must increasingly be taken into consideration as a cause of FUO.

Malignant lymphoma accounted for 12 of 26 cases of malignancy as a causative disease. In many cases, symptoms are not always severe and patients who present with fever or lymphadenopathy alone are often initially thought to have viral infections that are self-limiting, so more time may elapse before further invasive evaluation. With

malignant lymphoma as a cause of FUO, a mean of 2 months between fever onset and diagnosis has been reported (25). In 3 of the 12 patients with malignant lymphoma in our study, the times until diagnosis were 150 days, 190 days, and 250 days.

A comparison between patients ≥65 and <65 years old showed that infections were more common in patients <65 years old. This was influenced by the fact that this age group accounted for 16 of the 17 cases of HIV/AIDS and 10 of the 12 cases of infective endocarditis. Moreover, patients already diagnosed with HIV/AIDS at the time of fever development were excluded. The prevalence of NIID in patients ≥65 years old was greatly influenced by the ratio of polymyalgia rheumatica, which accounted for 7 of the 23 cases of NIID in patients ≥65 years old. Epidemiologically, it goes without saying that malignancy is more frequent among ≥65-year-old patients, and 8 of the 12 patients with malignant lymphoma were ≥65 years old. The prevalence of "other" causes in patients <65 years old was influenced by the greater incidences of necrotizing lymphadenitis (n=7) and subacute thyroiditis (n=5) in these patients. Unknown causes accounted for a high percentage of FUO cases, at 28.9% each in patients <65 years old and ≥65 years old, without any difference based on age.

The elderly population is expected to continue increasing, and this change will be particularly dramatic in Japan compared to other countries. According to demographic studies, 25% of persons in Japan are ≥65 years old, and 40% of the population in 2060 is expected to be ≥65 years old (26). Rates of diseases often seen in older adults such as polymyalgia rheumatica and malignancy will thus probably continue to increase. Polymyalgia rheumatica, as in the past, still requires time for diagnosis because there are no specific antibody tests, symptoms take time to develop, and other diseases must be ruled out. On the other hand, advances in imaging such as positron emission

tomography/computed tomography and genetic testing may enable earlier diagnosis of NIID such as temporal arteritis and Takayasu's arteritis, as well as malignancies. Comparison of the 10-year period between 1994 and 2003 and the 9-year period between 2004 and 2012 showed trends in causes of FUO based on time period. Age showed about the same distribution, and no significant biases were apparent with regard to sex. Infections and "other" causes decreased, whereas NIID, malignancy, and unknown causes increased. The trend in 2004-2012 was similar to that in the 1990s in an overseas report (22). Recent reports about classic FUO in Japan compared to those before 2000 show an increase in the percentage of unknown causes, stated as ≥20% of cases in all reports. Our study showed a similar trend (Table 4). The decrease in infections is probably due to earlier diagnosis with imaging and genetic testing, and because of the reduced frequency of patients with tuberculosis. The increase in malignancies was influenced by a greater number of malignant lymphomas in 2004-2012.

In 8 of the 256 patients, ≥150 days were required from the time of fever onset for diagnosis. The longest time was 325 days in a case of adult Still's disease. That patient was a 48-year-old man who had fever with mild lymphadenopathy and joint pain. However, these symptoms did not occur together, so time was required before a diagnosis could be reached. Starting about 1 month before diagnosis, the patient experienced joint pain, skin rash, and liver dysfunction, which led to the diagnosis. This study was a retrospective summary of cases, and each diagnosis was made by the treating physician at that specific time. Moreover, differences exist in regional and institutional features, and the fact that this is an urban university hospital and regional HIV center may have led to some biases. Among the 17 HIV-infected FUO cases in the

present study, 10 cases (58.8%) were diagnoses as infected with HIV before transfer to our hospital.

Further prospective studies are needed to follow FUO patients after hospital discharge and examine the outcomes. In addition, prospective studies should investigate causes of FUO in other than immunocompetent patients; for example, in patients with nosocomial, neutropenic, and HIV-related FUO.

Conclusion

This study reviewed patients with classic FUO evaluated at our hospital department since it was established. Our study found that together with the increase in HIV patients in Japan, HIV/AIDS is now the most common cause of FUO. In addition, the percentage of unknown causes of FUO has increased, now exceeding 20% of cases. As the present study collated data from a long period and reviewed the largest number of FUO cases in Japan to date, these findings will serve as a useful reference for the future care of FUO patients.

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Conflict of interest

None to declare.

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Tables

Table 1. Causes of classic FUO. HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; NIID, non-infectious inflammatory disease.

Table 2. Percentage of causes by category in patients ≥65 years old and <65 years old. NIID, non-infectious inflammatory disease.

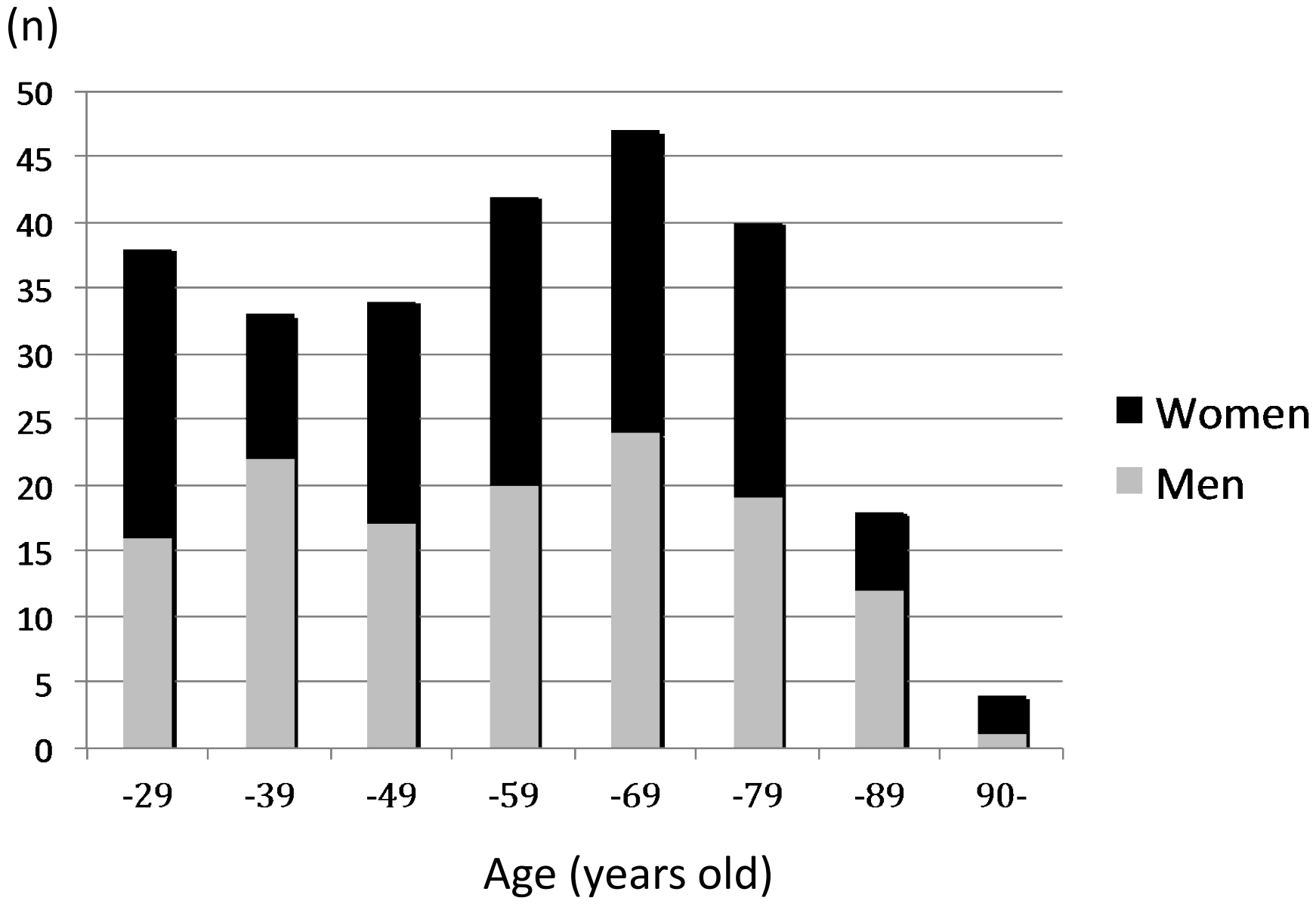
Table 3. Cases requiring ≥150 days from the time of fever onset for diagnosis. EBV, Epstein-Barr virus; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome.

Table 4. Comparison of results of studies of classic FUO in Japan. NIID, non-infectious inflammatory disease.

Figure legends

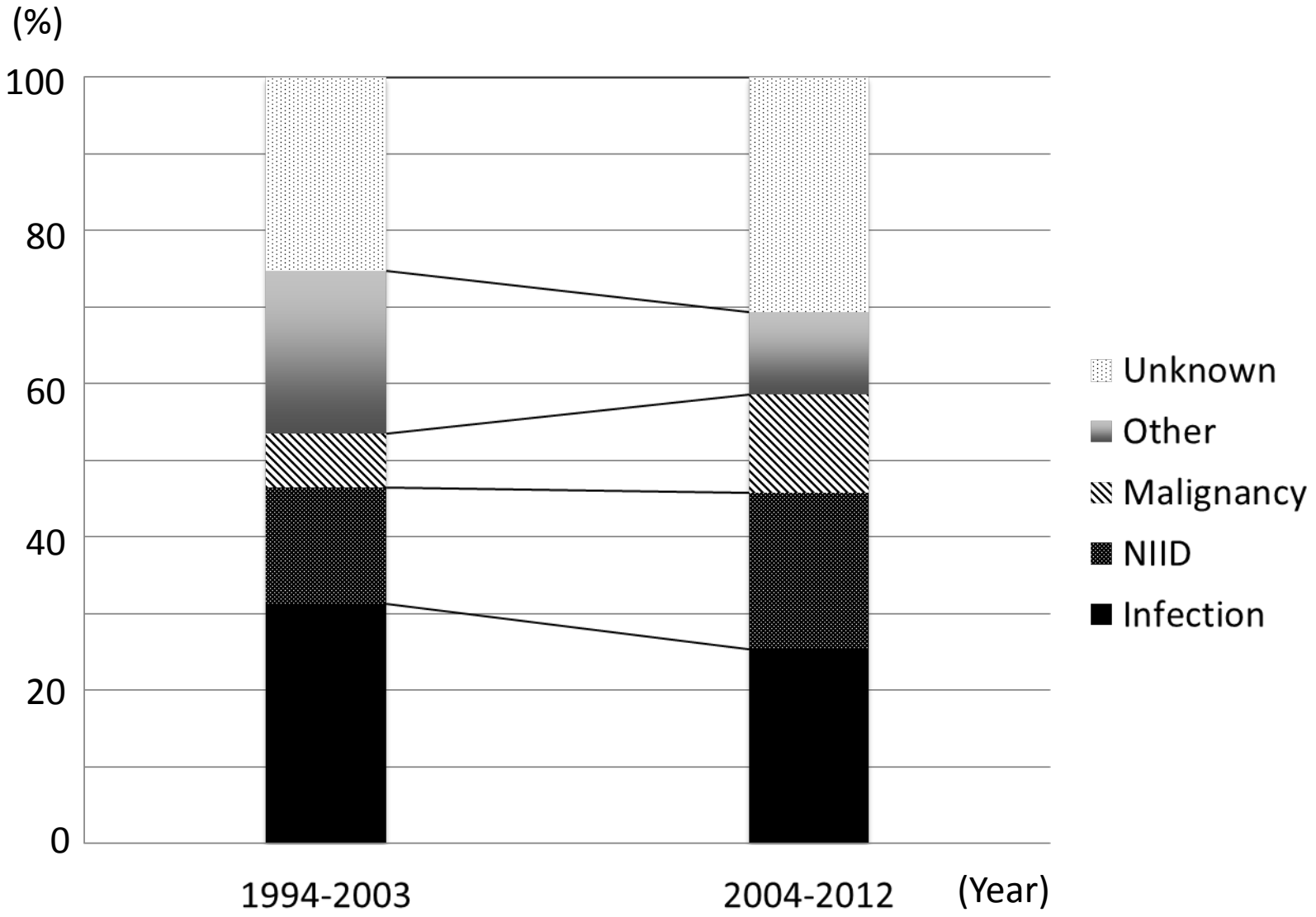
Figure 1. Age distribution.

Figure 2. Percentage of causes by category according to time period. NIID, non-infectious inflammatory disease.


(n)
50
45
40
35
30
25
20
15
10
5
0
-29
-39
-49
-59
-69
-79
-89
90-
Age (years old)
Women
Men

Causes	Number (%)
Infection	**71 (27.7%)**
HIV/AIDS	17
Infective endocarditis	12
Tuberculosis	4
Other	38
NIID	**47 (18.4%)**
Polymyalgia rheumatica	10
Adult Still’s disease	8
Reactive arthritis	5
Behçet’s disease	4
Other	20
Malignancy	**26 (10.2%)**
Malignant lymphoma	12
Other	14
Other	**38 (14.8%)**
Necrotizing lymphadenitis	7
Subacute thyroiditis	5
Other	26
Unknown	**74 (28.9%)**

	Total % (n)	≥65 years % (n)	<65 years % (n)
Infection	27.7 (71)	21.7 (18)	30.6 (53)
NIID	18.4 (47)	27.7 (23)	13.9 (24)
Malignancy	10.2 (26)	14.5 (12)	8.1 (14)
Other	14.8 (38)	7.2 (6)	18.5 (32)
Unknown	28.9 (74)	28.9 (24)	28.9 (50)
Total	100 (256)	100 (83)	100 (173)



Number	99	157
Median age (range)	55 (18-90)	55 (20-94)
Sex (number)	F44 M55	F80 M77

Causes	Duration (days)
Adult Still’s disease	325
HIV/AIDS	253
Malignant lymphoma	250
Takayasu’s arteritis	246
Chronic active EBV infection	243
Malignant lymphoma	185
HIV/AIDS	160
Macroglobulinemia	154
Malignant lymphoma	150

Reference	Year	n	Infection	NIID	Malignancy	Other	Unknown
14	1982-1992	153	28.8%	29.4%	14.4%	15.7%	11.8%
13	1986-1992	80	53.7%	16.2%	8.8%	3.8%	17.5%
16	2006-2007	81	35.8%	25.9%	9.9%	28.4%	
17	2011	56	21.4%	35.7%	7.1%	12.5%	23.2%
18	2011	121	23.1%	30.6%	10.7%	12.4%	23.1%
Present study	1994-2012	256	27.7%	18.4%	10.2%	14.8%	28.9%