Prognostic factors of Erdheim–Chester disease: a nationwide survey in Japan

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## Supplementary Data

### Supplementary Table S1. First signs and involved organs in the clinical course

| UPN | Age at onset | First signs       | Involved organs                                                                 | Outcome (survival year from onset) | REF |
|-----|--------------|-------------------|--------------------------------------------------------------------------------|------------------------------------|-----|
| 1   | 49           | Bone pain         | Bone, digestive organ (liver), kidney and retroperitoneal organ (renal infiltration), skin (erythema), breast, gingiva, lymph node | Alive (2.83+)                      | 1   |
| 2   | 44           | Xanthelasma       | Bone, cardiovascular system (LVH, PE, coated aorta), endocrine organ (hypopituitarism), kidney and retroperitoneal organ (hydronephrosis), skin (xanthelasma) | Dead (10.92)                       | 2,3 |
| 3   | 30           | Bone pain, DI, fever | Bone, cardiovascular system (palpitation), endocrine organ (DI)                  | Alive (6.92+)                      | 4,5 |
| 4   | 44           | Fever, malaise    | Bone, lung (interlobular septal thickening, cyst)                                | Dead (5.75)                        | N/A |
| 5   | 40           | DI                | CNS (exophthalmos), endocrine organ (DI)                                        | Dead (7.83)                        | N/A |
| 6   | 41           | Bone pain, fever  | Bone                                                                              | Alive (13.25)                      | 6   |
| 7   | 67           | Dyspnea           | Bone, cardiovascular system (cardiac tamponade, coated aorta), CNS (exophthalmos, spinal tumor), digestive organ (liver, pancreas), kidney and retroperitoneal organ (hydronephrosis), lung (pleural thickening and fibrosis), adrenal gland, bladder, spleen, testis | Dead (0.58)                        | N/A |
| 8   | 40           | Bone pain         | Bone, skin (papule)                                                              | Alive (10.08+)                     | N/A |
| 9   | 68           | Fever, malaise    | Bone, CNS (meningeal tumor), glottis                                              | Alive (1.08+)                      | N/A |
| 10  | 33           | Bone pain, fever  | Bone                                                                              | Alive (3.92+)                      | N/A |
| 11  | 68           | Bone pain, malaise | Bone                                                                              | Alive (3.75+)                      | N/A |
| 12  | 41           | Bone pain, vertigo | Bone, CNS (parenchymal mass)                                                     | Alive (6.50+)                      | N/A |
| 13  | 28           | DI, xanthelasma   | Bone, endocrine organ (DI), skin (xanthelasma)                                   | Alive (5.25+)                      | N/A |
| 14  | 56           | Low vision        | Cardiovascular system (coated aorta), CNS (exophthalmos), endocrine organ (hypothyroidism), kidney and retroperitoneal organ (hydronephrosis), skin (xanthelasma) | Dead (4.58)                        | 7   |
| 15  | 44           | Femoral tumor     | Skin (subcutaneous tumor)                                                        | Alive (1.00+)                      | N/A |
| 16  | 59           | Body weight loss  | Bone, cardiovascular system (coated aorta), endocrine organ (hypopituitarism), kidney and retroperitoneal organ (hydronephrosis), skin (xanthelasma) | Alive (3.58+)                      | N/A |
| 17  | 53           | Xanthelasma       | Bone, endocrine organ (DI), kidney and retroperitoneal organ, skin (xanthelasma) | Alive (5.33+)                      | N/A |
| 18  | 65           | DI                | Bone, cardiovascular system (heart failure, LVH, coated aorta), CNS (impaired consciousness), digestive organ (pancreatomegaly), endocrine organ (DI), kidney and retroperitoneal organ (hairy kidney), lung (details unknown) | Alive (2.75+)                      | N/A |
| #  | #  | Symptom | Organs/Affected Systems | Status | Notes |
|----|----|---------|-------------------------|--------|-------|
| 19 | 40 | Bone pain | Bone | Alive (10.08+) | N/A |
| 20 | 68 | Incidentally detected pulmonary infiltration | Bone, CNS (meningeal tumor), endocrine organ (pituitary tumor), cardiovascular system (heart failure), lung (centrilobular shadow, pleural thickening, fibrosis and pneumosclerosis) | Dead (4.50) | N/A |
| 21 | 45 | DI | Bone, CNS (cerebellar ataxia, exophthalmos), endocrine organ (DI), cardiovascular system (cardiac tamponade, mitral regurgitation, carotid stenosis), lung (cyst), kidney and retroperitoneal organ (retroperitoneal fibrosis, renal artery stenosis) | Alive (6.42+) | N/A |
| 22 | 67 | Dysarthria, vertigo, vomiting | CNS (cerebellar ataxia, meningeal tumor), kidney and retroperitoneal organ (hairy kidney) | Dead (0.25) | N/A |
| 23 | 46 | Dyspnea | Bone, cardiovascular system (heart failure, pulmonary hypertension), lung (interlobular septal thickening) | Dead (11.33) | N/A |
| 24 | 27 | Malaise | Bone, cardiovascular system (right atrial tumor), lung (cyst, obstructive disorder), kidney and retroperitoneal organ, skin (xanthelasma), gingiva, sinus | Alive (13.25+) | N/A |
| 25 | 46 | Bone pain | Bone, cardiovascular system (PE, coated aorta), CNS (parenchymal mass), digestive organ, endocrine organ (DI), kidney and retroperitoneal organ (hairy kidney, hydronephrosis) | Dead (3.58) | 8,9 |
| 26 | 49 | Dyspnea | Bone, lung (cyst, pleural thickening) | Alive (7.08+) | 10 |
| 27 | 25 | DI | Bone, endocrine organ (DI), kidney and retroperitoneal organ (hydronephrosis), skin (xanthelasma) | Dead (14.58) | 11, 12 |
| 28 | 76 | edema | Bone, CNS (papilledema), cardiovascular system (PE), kidney and retroperitoneal organ (hairy kidney), breast | Dead (2.25) | 13 |
| 29 | 40 | Amenorrhea, DI, malaise | Bone, CNS (parenchymal mass), endocrine organ (hypopituitarism), lung (detail unknown) | Alive (4.00+) | N/A |
| 30 | 62 | Fever, malaise | Bone, CNS (parenchymal mass), skin (tumor), oral mucosa | Dead (0.75) | N/A |
| 31 | 57 | Dyspnea, fever, general malaise | Bone, cardiovascular system (cardiac tamponade), kidney and retroperitoneal organ (hydronephrosis, peritoneal fibrosis) | Alive (6.67+) | N/A |
| 32 | 62 | Pericardial effusion | cardiovascular system (cardiac tamponade, right atrium tumor), CNS (subdural tumor), skin (xanthelasma) | Dead (4.33) | 14 |
| 33 | 48 | Bone pain | Bone, skin (xanthelasma) | Alive (21.08+) | N/A |
| 35 | 58 | Neck pain, numbness | Bone, CNS (parenchymal mass), kidney and retroperitoneal organ (hairy kidney, renal hypertension) | Alive (5.08+) | N/A |
| 36 | 72 | Bone pain, fever | Bone, cardiovascular system (PE, atrioventricular block), CNS (cerebellar ataxia), endocrine organ (hypopituitarism), kidney and retroperitoneal organ (hydronephrosis), skin (erythema) | Alive (1.67+) | N/A |
| 37 | 66 | Numbness | Bone, cardiovascular system (coronary artery disease, coated aorta), CNS (parenchymal mass), skin (xanthelasma), lymph node | Dead (1.83) | N/A |
| 38 | 67 | Dry cough, fever | Cardiovascular system (mitral regurgitation, right bundle branch block), CNS (pia mater involvement), digestive organ (liver, pancreas, esophagus, stomach, intestine, colon), endocrine organ (pituitary tumor), | Dead (0.83) | N/A |
| UPN | Age | Diagnosis | Comorbidities | Status   | Comment |
|-----|-----|-----------|---------------|----------|---------|
| 39  | 54  | Bone pain | Bone          | Alive (1.83+) | N/A     |
| 40  | 56  | Bone pain, fever | Bone, cardiovascular system (coronary artery disease, mitral regurgitation, coated aorta), CNS (parenchymal mass), endocrine organ (DI), kidney and retroperitoneal organ (hairy kidney), lung (interlobular septal and pleural thickening) | Dead (7.42) | N/A     |
| 41  | 47  | Bone pain, fever | Bone, cardiovascular system (pericarditis, coated aorta), CNS (exophthalmos), kidney and retroperitoneal organ (hydronephrosis), skin (phlebitis-like rash) | Dead (10.42) | N/A     |
| 42  | 66  | Bone pain, headache | Bone, cardiovascular system (coated aorta), CNS (meningeal and parenchymal tumor), endocrine organ (DI), kidney and retroperitoneal organ (hilar tumor), lung (interlobular thickening) | Alive (3.17+) | N/A     |
| 43  | 70  | Dyspnea  | Bone, cardiovascular system (PE), kidney and retroperitoneal organ (hairy kidney), skin (xanthelasma) | Alive (1.17+) | N/A     |
| 44  | 23  | Bone pain | Bone, cardiovascular system (right coronary invasion), CNS (parenchymal mass), endocrine organ (DI), kidney and retroperitoneal organ (hydronephrosis), lung (interlobular thickening) | Alive (11.08+) | N/A     |
| 45  | 68  | Bone pain, dyschezia | Bone, digestive organ (rectal tumor), prostate | Dead (0.83) | N/A     |

UPN indicates unique patient number; REF indicates Supplemental references listed below and N/A indicates that no article about the patient has been reported; CNS indicates central nervous system; DI indicates diabetes insipidus; PE indicates pericardial effusion; LVH indicates left ventricular hypertrophy.
**Supplementary Table S2. Cause of death**

| UPN | Cause of death                     |
|-----|-----------------------------------|
| 2   | Unknown                           |
| 4   | ECD                              |
| 5   | Unknown                           |
| 7   | Arrhythmia                        |
| 14  | Renal failure                     |
| 20  | Pneumonia                         |
| 22  | Brain hypertension                |
| 23  | Respiratory failure               |
| 25  | Heart and renal failure           |
| 27  | Unknown                           |
| 28  | ECD                              |
| 30  | Infection                         |
| 32  | Heart failure                     |
| 37  | Invasive pulmonary aspergilosis   |
| 38  | Sepsis due to rectal perforation  |
| 40  | Heart failure                     |
| 41  | Heart failure                     |
| 45  | ECD                              |

ECD indicates Erdheim–Chester disease;
## Supplementary Table S3. **BRAF** mutation status of clinical samples

| UPN | Type of sample       | Sanger sequencing | BRAF mutation status of each patient |
|-----|----------------------|-------------------|-------------------------------------|
| 1   | Skin                 | V600E             | Mutation                            |
|     | Bone                 | V600E             |                                     |
| 2   | Skin                 | V600E             | Mutation                            |
|     | Skin                 | V600E             |                                     |
| 3   | Bone                 | V600E             | Mutation                            |
| 7   | Heart                | V600E             | Mutation                            |
| 8   | Tumor                | V600E             | Mutation                            |
|     | PB (control)         | Wild              |                                     |
| 11  | Bone                 | V600E             | Mutation                            |
|     | PB (control)         | Wild              |                                     |
| 16  | Skin                 | Wild              | Mutation                            |
|     | Bone                 | V600E             |                                     |
|     | PB (control)         | Wild              |                                     |
| 21  | Bone                 | Wild              | Wild                                |
|     | PB (control)         | Wild              |                                     |
| 24  | Skin                 | V600E             | Mutation                            |
| 29  | Lung                 | Wild              | Wild                                |
|     | PB (control)         | wild              |                                     |
| 35  | Brain                | Wild              | Wild                                |
|     | Bone marrow (control)| Wild              |                                     |
| 36  | Skin                 | V600E             | Mutation                            |
|     | PB (control)         | Wild              |                                     |
| 39  | Bone                 | V600E             | Mutation                            |
| 44  | Bone                 | V600E             | Mutation                            |
|     | PB (control)         | Wild              |                                     |

UPN indicates unique patient number and PB, peripheral blood. Wild means **BRAF**V600E mutation is absent.
Supplementary Figure S1. Duration between first sign of Erdheim-Chester disease and diagnosis. Patient number is shown according to the duration (months).
Supplementary Figure S2. Survival curve of patients with Erdheim–Chester disease. Kaplan–Meier estimation for survival from onset based on presence of (A) endocrine involvement, (B) pulmonary involvement, (C) retroperitoneal involvement, (D) cutaneous lesion, and (E) cardiovascular involvement. CV indicates Cardiovascular lesion.
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