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Extensive multiple organ involvement in VEXAS syndrome

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Authorship Criteria

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Clinical Images

A 55-year-old Japanese man was diagnosed with VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, which is a newly documented adult-onset autoinflammatory disease caused by somatic *UBA1* mutations [1], after four years of symptoms. He had suffered from recurrent fever after the onset of systemic arthralgia, scleritis, periorbital/orbital inflammation, optic perineuritis **(A, B,** T1-weighted contrast-enhanced magnetic resonance imaging in **C** and **D, arrow** in **D)**, and myelodysplastic syndrome. Each bout of fever had lasted four days, reaching 42°C, with systemic arthralgia and painful/painless erythema with ulceration **(E, F)**. Computed tomography (CT) showed pulmonary infiltration **(H)** with an acute inflammatory reaction (C-reactive protein, 7.21 mg/dL maximum). Skin biopsies from erythematous lesions revealed leukocytoclastic vasculitis with neutrophil and lymphocyte infiltration in the superficial dermis **(G)**. Pancytopenia with macrocytic anemia gradually progressed. Bone marrow aspirate smears consistently revealed multilineage dysplasia without excess blasts **(K)**, and the chromosomes showed a consistently normal karyotype. Myeloid precursor cells showed cytoplasmic vacuoles **(K, L)**. We extracted genomic DNA from peripheral blood from the patient and his mother. In the patient, whole-exome sequencing identified the heterozygous nonsynonymous substitution c.121A>G (p.Met41Val) in *UBA1* [2], confirmed by Sanger sequencing. The mutation was not detected in his unaffected mother. We found no structural variations in the X chromosome, nor potentially pathogenic mutations in other genes implicated in autoinflammatory diseases/myelodysplastic syndromes. The symptoms were refractory to moderate doses of corticosteroids (prednisolone 0.5 mg/kg/day), tocilizumab, canakinumab, and etanercept. CT showed granular shadows and ground-glass opacity and the patient had severe dyspnea, which were not seen during the usual attack. The pneumonia quickly disappeared after drug discontinuation without any additional therapy, suggesting hypersensitivity pneumonia from canakinumab **(I)** and etanercept **(J)** administration, although we cannot exclude the possibility that the pneumonia was just a natural progression of the disease. Bone scintigraphy revealed that the systemic arthralgia at onset **(M)** had progressed to systemic arthritis after four years **(N)**. Previously undescribed symptoms such as severe orbital inflammation, undiagnosed arthritis, and hypersensitivity reaction to canakinumab and etanercept suggest that the syndrome involves more multiple organ involvement than reported [1, 3].

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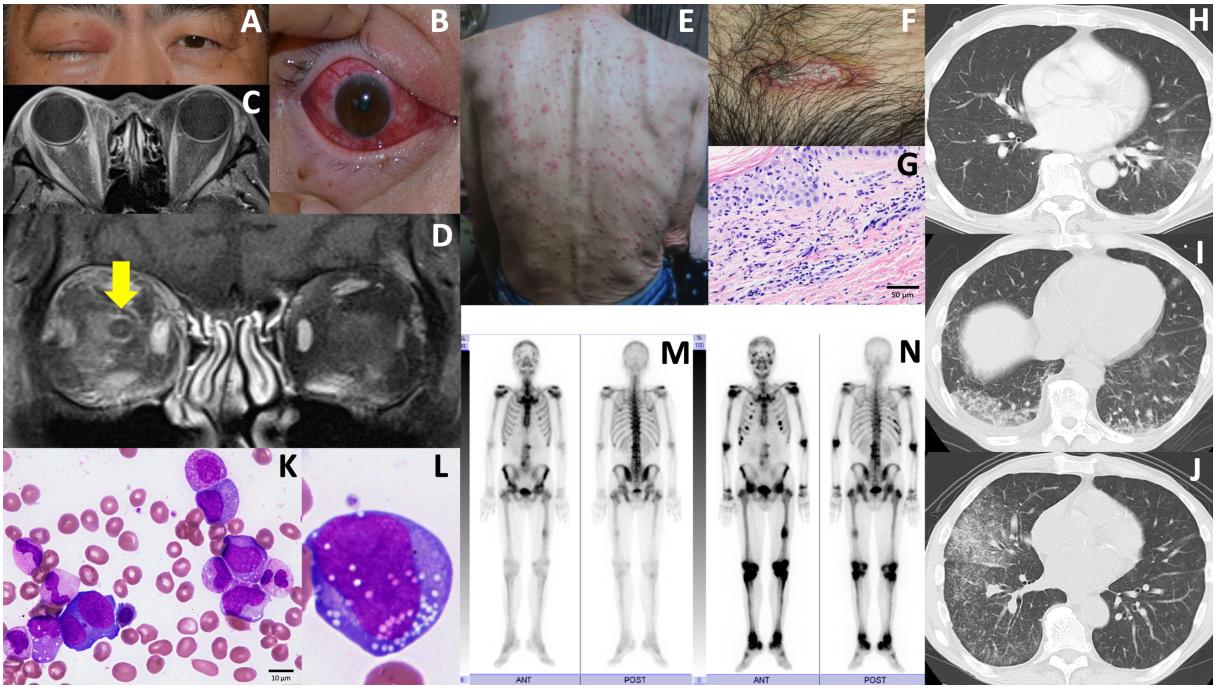

Figure 338x190mm (300 x 300 DPI)