Letters to the Editors

Detection of anti-neutrophil cytoplasmic and antinuclear autoantibodies favouring misdiagnoses in 5 cases of Erdheim-Chester disease

Sirs,

Erdheim Chester disease (ECD) is a rare non-Langerhans cell histiocytosis affecting one or multiple organs (1). Although any organ can be affected, involvement of the central nervous system (CNS), orbit, heart, lung, retroperitoneum, bones and skin is most frequently encountered in ECD (1-4). Classification of ECD according to predominant affection of one organ system or multisystem ECD is used (3). A high prevalence of activating kinase mutations such as *BRAF V600E* suggests clonal expansion of histiocytes as the underlying cause of ECD (1, 5). A marked infiltration with foamy mononucleated CD68-positive, CD1a and S100 negative histiocytes is the distinctive histopathologic feature of ECD (1). Diagnostic criteria include characteristic histological findings and evidence of skeletal abnormalities on x-ray and bone scintigraphy (6).

Between March 2015 and 2017, we diagnosed five consecutive cases of loco-regionally dominant ECD (Table I). Isolated CNS lupus had been initially discussed as a potential differential diagnosis in patient 1 before. In patients 2, 4 and 5, the preexisting diagnoses were undifferentiated connective tissue disease or Sjögren's syndrome. Finally, ANCA-associated vasculitis had formerly been assumed in patient 3. All patients had insufficiently responded to previous treatment with either prednisolone alone or in combination with methotrexate or azathioprine. Based upon reevaluation of the patients' medical history, their disease course and request of specified immunohistochemistry and *BRAF V600E* mutation analysis of resected tissues, we reclassified the disease as ECD in patients 1–5. Time from first manifestation to diagnosis of ECD was 107 months (median; range 3 – 228 months) in our cohort as compared to a recently reported mean time to diagnosis of 51 months (2). The rarity of ECD often impedes a timely diagnosis and requires a high degree of suspicion. A delay before diagnosis of up to 25 years was noted in another study (6). Incidental detection of antinuclear autoantibodies (ANA), but not anti-neutrophil cytoplasmic autoantibodies (ANCA) has been reported in ECD previously (2). Notably, testing for extractable nuclear antigen antibodies (ENA) and different antigen-specificities of ANCA including myeloperoxidase (MPO) and proteinase 3 (PR3) was negative in our patients. In another case series, autoimmune diseases were suspected in 27% and vasculitis 22% of the patients; other misdiagnoses were sarcoidosis, lymphoma, and brain- and bone-cancer (2).

After reclassification and diagnosis of ECD in our patients, we followed the consensus guidelines for the diagnosis and management of ECD (3). Remission was induced with interferon-α in four of our patients, while an increase of the azathioprine dosage was sufficient to control disease in the fifth. Interferon-α and anti-cytokine directed therapies have been recommended as first-line treatment in ECD (3, 7). Vemurafenib may represent an alternative in those >50% of patients with *V600E BRAF* mutation (8).

F. Özden[1], *MD*
S. Schinke[1], *MD*
C. Thorns[2], *MD*
T. Eckey[3], *MD*
K. Dalhoff[4], *MD*
T.F. Münte[5], *MD*
V. Tronnier[6], *MD*
J.Y. Humrich[1], *MD*
G. Riemekasten[1], *MD*
P. Lamprecht[1], *MD*

[1]Department of Rheumatology and Clinical Immunology, University of Lübeck; [2]Institute for Pathology, Cath. Mary's-Hospital, Hamburg; [3]Institute for Neuroradiology, University of Lübeck; [4]Department of Internal Medicine III – Pulmonology, University of Lübeck; [5]Department of Neurology, University of Lübeck; [6]Department of Neurosurgery, University of Lübeck, Germany.

Please address correspondence to:
Dr Filiz Özden,
University of Lübeck,
Ratzeburger Allee 160,
23538 Lübeck, Germany.
E-mail: filiz.oezden@uksh.de

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Table I. Clinical manifestations in 5 patients with Erdheim Chester disease (ECD).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Final diagnosis	CNS dominant ECD	Cardiac dominant ECD	Orbital-craniofacial dominant ECD	Orbital-craniofacial dominant ECD	Orbital-craniofacial dominant ECD
Age (years)	64	73	61	59	62
Clinical manifestations and medical imaging	Homonymous hemianopsia (occipital lesion) and amaurosis (optic nerve lesion)	Chronic pericardial effusion, metaphysodiaphyseal sclerosis of femur and tibia	Orbital and nasolabial swelling, peri-bronchitis	Orbital and facial swelling	Orbital swelling, metaphysodiaphyseal sclerosis of tibia
Auto-antibody	ANA 1:10240	ANA 1:320, centromere ab.	P-ANCA 1:160	ANA 1:320	ANA 1:160
BRAF V600E mutation	Negative	Positive	Negative	Negative	Negative
Surgical procedures before diagnosis	Resection of cerebral lesion	Pericardiocentesis and ectomy	Repetitive resections of nasolabial tumescence	Resection of orbital tumescence	Resection of orbital tumescence
Treatment following diagnosis of ECD	Interferon-α	Interferon-α	Interferon-α	Azathioprine	Interferon-α

ANA: anti-nuclear autoantibody; P-ANCA: perinuclear anti-neutrophil cytoplasmic autoantibody.