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Case Report
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Indeterminate Dendritic Cell Tumor With Persistent Complete Metabolic Response to BRAF/MEK Inhibition

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Indeterminate dendritic cell tumor (IDCT) is a very rare entity within the class of histiocytic and dendritic neoplasms. According to the classification of the histiocyte society, it is referred to as indeterminate cell histiocytosis within the Langerhans (L) group of histiocytoses. IDCT often manifests with skin lesions and less common with nodal and splenic manifestations. The cells of origin are believed to be indeterminate cells, which are precursors of L cells.[1,2] Accordingly, IDCT typically shows incomplete expression of L cell markers with positivity for S100 and CD1a but lacking Langerin (CD207). Moreover, histiocytic markers, markers for follicular dendritic cell sarcomas, B and T cells are negative. Regarding Langerin, the lack of its expression probably does not totally exclude L cell histiocytosis (LCH).[3] In ultrastructure, Birbeck granules are negative. Genetically recurrent ETV3-NCOA2 translocations have been reported in IDCT.[4] For several entities within the class of histiocytic and dendritic neoplasms *BRAF* p. V600E was described, most frequently for LCH and Erdheim-Chester disease (ECD). In LCH lacking this specific mutation, *BRAF* gene fusions and small in-frame deletions of *BRAF* as well as downstream mutations in *MAP2K1* or *MEK1* have frequently been reported.[5-8] For IDCT, 1 case with *BRAF* V600E mutation was published.[9] An association with lymphoma and leukemia is known for both LCH and IDCT as for several related diseases.

Here we report a case of a 57-year-old male patient, who was referred to us by the department of orthopedics. For about 2 years, the patient had noticed pain in the area of the right elbow with increasing functional impairment. At presentation, he described a pain of 7 on visual analogue scale with radiation to the right shoulder. Furthermore, he complained of a new pain in the area of the costal arch, requiring metamizole and nonsteroidal anti-inflammatory drugs as analgesia. Moreover, he had strong night sweats, but neither loss of weight nor fever. Clinical examination showed a slightly reduced general state (Eastern Cooperative Oncology Group 1), a normosomal nutritional status and a severe swelling of the right upper arm and lymph nodes in the shoulder area. Further physical examination was regular.

An open biopsy of the right humerus showed bone and soft tissue with partly aggregated, relatively large cells with well-delineated cell borders, eosinophilic cytoplasm, and slightly pleomorphic and enlarged nuclei with enlarged nucleoli and infrequent mitoses. Immunohistochemically, the cells reacted with antibodies against CD1a, S100, but were negative for Langerin and negative for B-cell and T-cell markers. The lesional cells had a Mib-1 proliferation index of 20%-30%. The reference pathologist concluded that the histiocytic morphology in combination with the expression of CD1a and partially S100 in the absence of expression of Langerin ensured the diagnosis of IDCT (Figure 1). Differential diagnoses with clinical profiles, IHC, and genetic profiles are presented in the Table 1.

IDCT is an extremely rare neoplasm with variable clinical course and similar to other histiocytic/dendritic neoplasms, it is frequently associated with B-cell lymphomas or myeloid neoplasms.[10,11]

Bone marrow biopsy showed no evidence of a lymphoproliferative disease, leukemia, or infiltration of a dendritic histiocytic neoplasia. Since the magnetic resonance imaging (not shown) already showed evidence of systemic spread to axillary and hilary lymph nodes and pulmonary metastases, which was confirmed in the [^{18}F]fluorodeoxyglucose positron emission tomography/computer tomography (Figure 2), a resection was not possible. Due to the frequent occurrence of *BRAF* mutations in the closely related LCH[12] and 1 published case of *BRAF* V600E in IDCT,[9] description of *BRAF* V600E in other histiocytosis like Rosai Dorfman disease,[13] which are normally not associated with this

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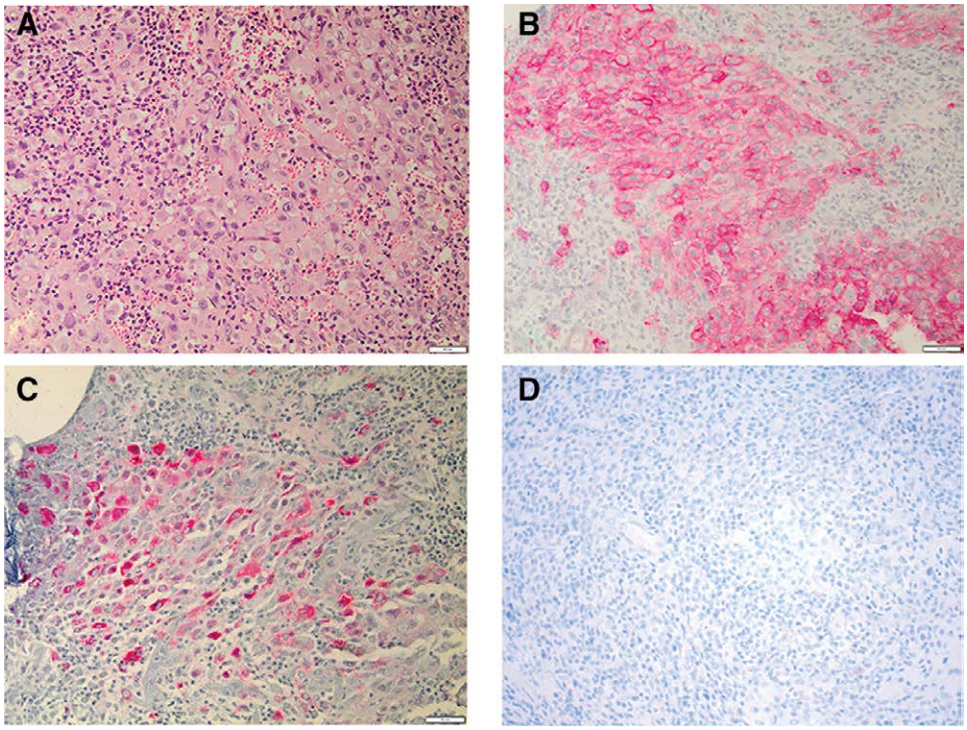

Figure 1. Histology and immunohistochemistry of IDCT case. The H&E showed partly aggregated, relatively large cells with well-delineated cell borders (A), which were positive for CD1a (B) and S100 (C) while being negative for Langerin (D). H&E = hematoxylin and eosin.

Table 1

Clinical Profile, Immunohistochemistry, and Genetics of Histiocytic and Dendritic Neoplasms.

Disease	Clinical Profile	IHC and Ultrastructure	Genetic Alterations
LCH	Incidence: 5/100,000/y; most childhood, male predominance. Solitary or multiple lesions mostly bone and/or adjacent soft tissue. Less frequent nodal and skin. Subgroup of primary LCH of lung in smokers. HLH can occur as complication in LCH. Association with lymphoma. High-grade variant Langerhans cell Sarcoma.	• Langerhans cell markers: CD1a^{++}, Langerin (CD207)$^{++}$, S100^{++}. • CD68^{+} Vimentin^{+}, HLA-DR^{+}, CD4^{+} • Negative for: T-cell and B-cell markers, FDC markers (CD21^{-}, CD35^{-}, and CD23^{-}), and histiocytic marker: CD163 • Ultrastructure: presence of cytoplasmic Birbeck granules	BRAF V600E 50%. Primary lung LCH: 28% with BRAF V600E. In BRAF wild type often mutations in MAP2K1 or ARAF genes. 30% clonal IGH, IGK, TCR genes.
IDCT: Synonyms: ICH	Incidence: extremely rare Typically, singular or multiple papules, nodules, or plaques on the skin; less often primary lymph node or splenic disease	• Langerhans cell markers: CD1a^{+}, S100^{+}, Langerin^{-} • Histiocytic marker: CD163^{-} • Negative for T-cell and B-cell markers and FDC markers (CD21^{-}, CD35^{-}, and CD23^{-}) • Ultrastructure: interdigitating processes, but no Birbeck granules	At least 1 case described with BRAF V600E
ECD	Rare, mean age 55-60 y. Skeletal infiltration: ≥95%, cardiovascular manifestation: 50%, retroperitoneal manifestation: 1/3 cases, CNS involvement: 20%-30%; cutaneous manifestation with typical Xanthelasma.	• Histiocytes with foamy, xanthomatous cytoplasm, Touton cells. • Macrophage markers: CD14^{+}, CD68^{+}, CD163^{+} • Langerhans cell markers: S100^{-}, CD1a^{-}, Langerin^{-}, some may express S100. • Lesions of LCH within ECD in 20%. • Ultrastructure: no Birbeck granules	BRAF V600E > 50% cases, mutations in PI3KCA and NRAS
Diffuse juvenile xanthogranulomatosis	Solitary skin involvement more frequent, than other forms. Soft tissue with predilection of head and neck region. Mucosal surfaces in particular aerodigestive tract. CNS, dura, pituitary stalk, bone marrow.	• Progressively lipidous, foamy Touton-type (xanthomatous) giant cells • Macrophage markers positive: CD14^{+}, CD68^{+}, CD163^{+}, • Langerhans cell markers: S100^{+} ≤ 20%, CD1a^{-}, Langerin^{-} • Mixed inflammatory infiltrate	Association with NF type 1, no BRAF mutations described.
RDD*	Lymphadenopathy, mostly cervical. RDD is clinically classified as familial or sporadic. Further categories are: classical (nodal), extranodal, associated with neoplasm or immune disease	• Large histiocytic cells with hypochromatic nuclei and pale cytoplasm, often emperipolesis • Fascin^{+} • macrophage markers: CD68^{++}, CD14^{+}, HLA-DR^{+}, CD163^{+} • Langerhans cell markers: S100^{+}, CD1a^{-}, Langerin^{-} • Frequently IgG4-positive plasma cells	

(*Continued*)

Table 1
(*Continued*)

Disease	Clinical Profile	IHC and Ultrastructure	Genetic Alterations
IDC	Incidence: extremely rare; most frequently asymptomatic solitary lymph node, less frequently extralymphatic manifestation in skin and soft tissue	• Fascin^{++}, Vimentin+ • Langerhans cell markers: CD1a^{-}, Langerin^{-}, S100^{+} • FDC markers: CD21^{-}, CD35^{-}, and CD23^{-} • Ultrastructure: no Birbeck granules	Possible transdifferentiation of indolent lymphoma. One reported case with BRAF mutation
FDC	Incidence: rare, adult predominance. Mostly localized disease. Lymph node 31%, extranodal 58%, nodal and extranodal 10%. Slowly growing, often large mass. Association with Castleman disease lesion.	• FDC markers: CD21^{+}, CD35^{+}, and CD23^{+} • Langerhans cell markers: S100$^{+/-}$, CD1a^{-} • Macrophage markers: CD163^{-}, CD68$^{+/-}$ • Ultrastructure: elongate nuclei with invaginations, no Birbeck granules	Frequent clonal Ig rearrangements, BRAF mutation 0%-19%

CNS = central nervous system; ECD = Erdheim-Chester disease; FDC = follicular dendritic cell sarcoma; HLH = haemophagocytic lymphohistiocytosis; ICH = indeterminate cell histiocytosis; IDC = interdigitating dendritic sarcoma; IDCT = indeterminate dendritic cell tumor; IHC = immunohistochemistry; LCH = Langerhans cell histiocytosis; NF = neurofibromatosis; RDD = Rosai Dorfman disease.
*Not listed in WHO 2016 classification.

mutation, and effectivity of BRAF inhibition with vemurafenib in LCH or ECD with *BRAF* V600E,[14,15] targeted sequencing for a *BRAF* mutation was requested and a V600E mutation was indeed detected in our patient by Sanger sequencing with an allele frequency of 20%-30%. In the absence of a standard therapy for IDCT, a targeted therapy with BRAF/MEK inhibition with dabrafenib 150 mg twice per day and trametinib 2 mg per day was initiated. Three months later, an [^{18}F]FDG/PET scan showed a complete metabolic remission (Figure 3). This was accompanied by a remarkable improvement of his general condition and the patient could resume sports activities. [^{18}F]FDG/PET controls confirmed a persisting complete metabolic remission for >1 year (Figure 3). This case affirms the occurrence of *BRAF* V600E in IDCT and demonstrates for the first time a very good response to targeted therapy (sustained complete metabolic response) in this rare disease.

Unfortunately, 14 months after initiation of BRAF/MEK1/2 inhibition, the patient developed an acute kidney failure during summer month within an extraordinary heat period, to which very likely BRAF inhibition contributed as this represents a well-known adverse event; however, lower incidences were reported after addition of MEK-coinhibition.[16-18] Our patient is on regular hemodialysis, continued combined BRAF/MEK inhibition in reduced dose and is in ongoing complete metabolic remission 23 months after initiation of therapy documented by a [^{18}F]FDG/PET control (not shown).

From other histiocytosis it is known that cessation of BRAF/MEK inhibition provokes relapse, for example, 75% of patients

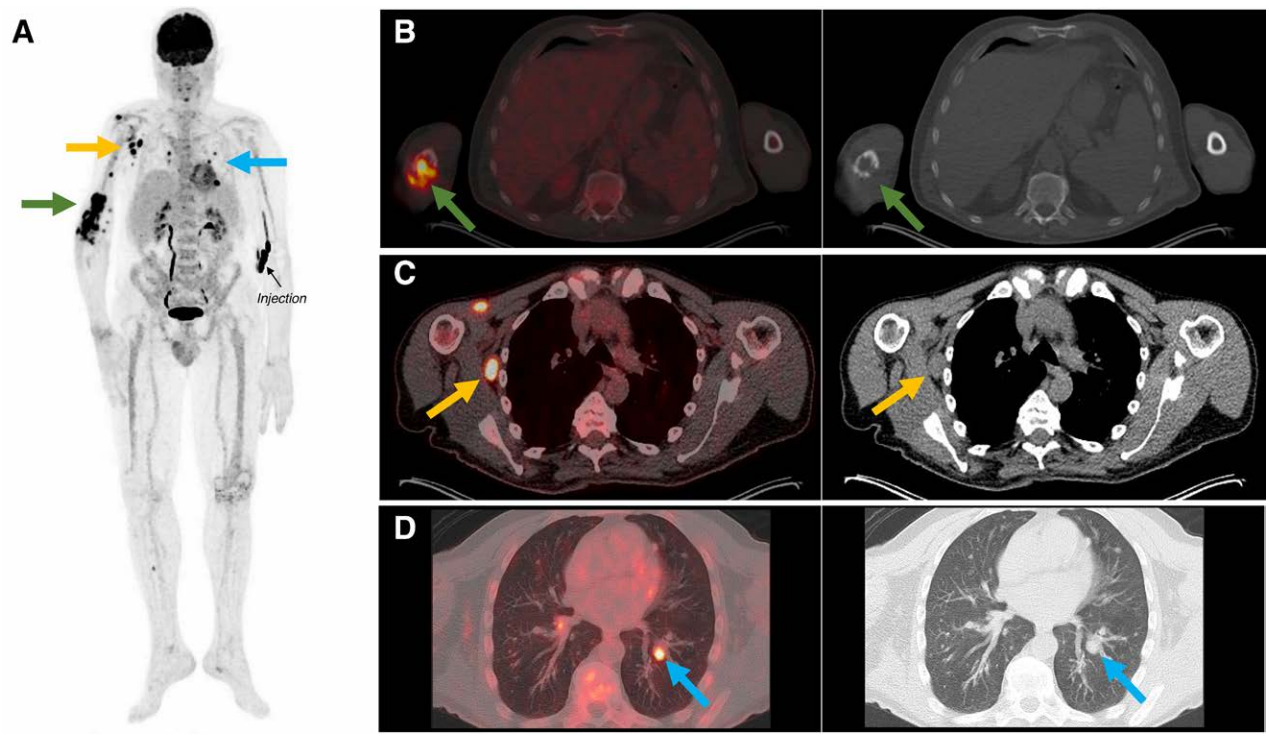

Figure 2. Initial [^{18}F]FDG-PET/CT showing metastatic disease. (A), MIP. (B–D), Transaxial slices of PET/CT fusion and CT with exemplary metastases). Osteolytic manifestation in the right distal humerus indicated by green arrow (B [left]: PET/CT fusion showing high [^{18}F]FDG uptake with SUVpeak of 13.3; B [right]: CT scan showing osteolytic lesion). Further skeletal lesions were present at the right acromion, the 10th rib left dorsal, the sternum, the sacrum, and in the right tibia. The yellow arrow indicates lymph node metastases on the right axillary region (C). Further lymph node metastases were found hilary. Moreover, multiple pulmonary metastases were found, exemplary indicated by blue arrow (D). [^{18}F]FDG-PET/CT = fluorodeoxyglucose positron emission tomography/computer tomography; MIP = maximum intensity projection; SUV = standardized uptake value.

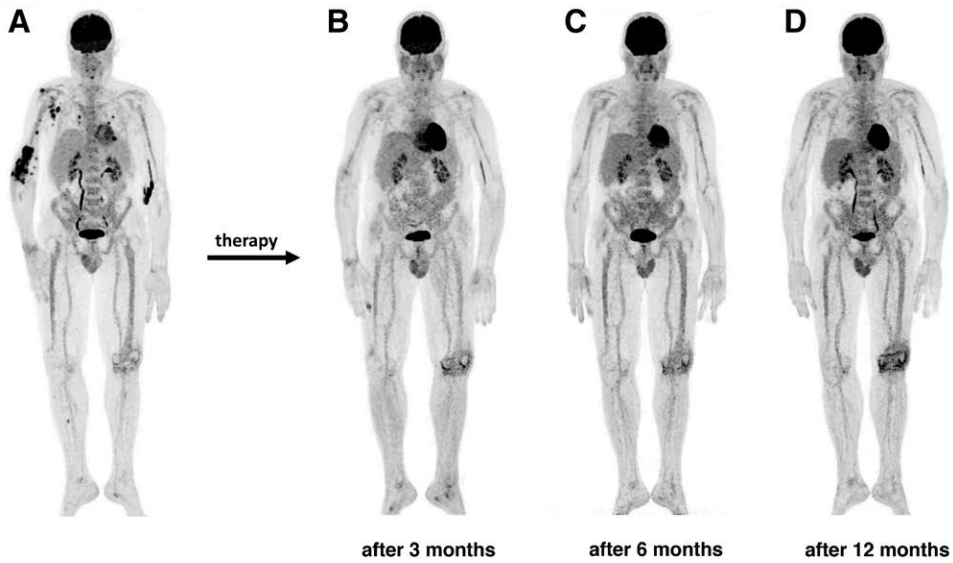

Figure 3. Persistent complete metabolic remission by BRAF/MEK inhibition. MIP of [18F]FDG-PET/CT (A: initial disease, B–D: controls after therapy). Three months after initiating dabrafenib/trametinib, a complete metabolic remission was observed (B). This complete metabolic remission persisted for 1 y (C, D). As an additional finding, increasing [18F]FDG uptake was found in the left knee joint consistent with a synovialitis following total knee arthroplasty. [18F]FDG-PET/CT = fluorodeoxyglucose positron emission tomography/computer tomography; MIP = maximum intensity projections.

with ECD developed a relapse with a median time to relapse of 6 months.[19]

Even if it is only a single case, we recommend to consider an analysis for BRAF mutations in histiocytic and dendritic neoplasms, to enable possible targeted therapeutic approaches, considering the very good results in LCH and ECD.[14,15] Looking at this in a broader context independent of dendritic-histiocytic neoplasms, recently published results of histology-independent targeted therapy for BRAF V600-mutated refractory/relapsed neoplasia pointed in the same direction.[20]

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127:2375–2390.
2. Emile JF, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*. 2016;127:2672–2681.
3. Chabrol E, Thépaut M, Dezutter-Dambuyant C, et al. Alteration of the langerin oligomerization state affects Birbeck granule formation. *Biophys J.* 2015;108:666–677.
4. Brown RA, Kwong BY, McCalmont TH, et al. ETV3-NCOA2 in indeterminate cell histiocytosis: clonal translocation supports sui generis. *Blood*. 2015;126:2344–2345.
5. Chakraborty R, Burke TM, Hampton OA, et al. Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis. *Blood.* 2016;128:2533–2537.
6. Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood.* 2014;124:3007–3015.
7. Brown NA, Furtado L V., Betz BL, et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. *Blood.* 2014;124:1655–1658.
8. Nelson DS, Quispel W, Badalian-Very G, et al. Somatic activating ARAF mutations in Langerhans cell histiocytosis. *Blood.* 2014;123:3152–3155.
9. O'Malley DP, Agrawal R, Grimm KE, et al. Evidence of BRAF V600E in indeterminate cell tumor and interdigitating dendritic cell sarcoma. *Ann Diagn Pathol.* 2015;19:113–116.
10. Vener C, Soligo D, Berti E, et al. Indeterminate cell histiocytosis in association with later occurrence of acute myeloblastic leukaemia. *Br J Dermatol.* 2007;156:1357–1361.
11. Ventura F, Pereira T, Duarte MDL, Marques H, Pardal F, Brito C. Indeterminate cell histiocytosis in association with acute myeloid leukemia. *Dermatol Res Pract*. 2010;2010:569345.
12. Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. *Blood.* 2012;120:2700–2703.
13. Fatobene G, Haroche J, Rodzwicz ZH, et al. BRAF V600E mutation detected in a case of Rosai-Dorfman Disease. *Haematologica.* 2018;103:e377–e379.
14. Haroche J, Cohen-Aubart F, Emile JF, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. *Blood.* 2013;121:1495–500.
15. Cohen-Aubart F, Charlotte F, Idbaih A, et al. Long-term outcome of 117 patients with Erdheim-Chester disease and mixed histiocytosis receiving targeted therapies (BRAF and MEK inhibitors): a monocentric experience. *J Clin Oncol.* 2017;264:891–897.
16. Jhaveri KD, Sakhiya V, Fishbane S. Nephrotoxicity of the BRAF inhibitors vemurafenib and dabrafenib. *JAMA Oncol.* 2015;1:1133–1134.
17. Launay-Vacher V, Zimner-Rapuch S, Poulalhon N, et al. Acute renal failure associated with the new BRAF inhibitor vemurafenib: a case series of 8 patients. *Cancer.* 2014;120:2158–2163.
18. Teuma C, Pelletier S, Amini-Adl M, et al. Adjunction of a MEK inhibitor to vemurafenib in the treatment of metastatic melanoma results in a 60% reduction of acute kidney injury. *Cancer Chemother Pharmacol.* 2017;79:1043–1049.
19. Cohen Aubart F, Emile JF, Carrat F, et al. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). *Blood*. 2017;130:1377–1380.
20. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAF V600E/K mutations: results from the molecular analysis for therapy choice (MATCH) Arm H. *J Clin Oncol.* 2020;37:3002–3002.