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Case report

Erdheim-Chester disease with novel gene mutations discovered as an incidental finding in explanted liver of a patient with hepatitis C cirrhosis: A case report and literature review

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ABSTRACT

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis characterized by xanthogranulomatous infiltration of foamy histiocytes frequently involving bone and other organ systems. We herein report a unique case of ECD discovered incidentally in an explanted liver in a 65-year-old male with end-stage liver disease secondary to hepatitis C cirrhosis. Histological examination and immunohistochemical studies in the explanted liver revealed prominent foamy histiocytes that were CD68 positive, but CD1a and S100 negative. Mutational hotspot analysis of the explanted liver using a panel of 47 most common cancer-related genes performed by next generation sequencing (NGS) revealed likely somatic mutations in the *PDGFRA*, *PTEN*, and *HNF1A* genes, but no *BRAF* codon 600 mutations were detected. The bone marrow showed similar findings as in the liver. Whole body PET and bone scans demonstrated increased heterogeneous uptake in bilateral humeral and femoral diaphysis, most compatible with ECD. To our knowledge, this is the first case report of ECD that involves mainly bone marrow and liver with novel genomic alterations. Our case highlights the diversity and complexity of this disease entity and the importance of multi-modality approach integrating clinical and radiologic features with histopathologic and molecular/genomic findings.

1. Introduction

First described in 1930 by Drs. Jakob Erdheim and William Chester as "lipioid granulomatosis", Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis characterized by xanthogranulomatous infiltration with foamy histiocytes [1–3]. It affects middle-aged individuals with a slight male predominance. As of the present time, approximately 400 cases of ECD have been documented, the majority of which have been reported in the last 10 years. Skeletal involvement causing bone pain occurs in the vast majority of cases (up to 96%), and manifests typically as osteosclerosis of the long bones on imaging studies [4]. Approximately half of those affected have extraskeletal involvement, including the hypothalamus-pituitary axis [5], lung [6], heart [7], gastrointestinal (GI) tract [8], retroperitoneum [9], skin [10], kidneys [11], spleen [12], and orbit [13], etc. As a result, the symptoms of ECD can be general or focal, and the clinical course is diverse ranging from indolent disease to a systemic syndrome of rapid progression, with a reported global 5-year mortality of 30–40% [14]. The diagnosis of ECD relies on typical histomorphological findings, supported by immunohistochemical studies to confirm monocyte origin of the lesional cells [15–17]. ECD can be elusive given its rarity, variable organ involvement, and non-specific clinical presentation.

While the exact etiology of ECD is as yet unknown, accumulated evidence so far has supported the notion that at least some cases of ECD represent a clonal disorder based on the reported mutations including BRAF V600E [18–21], *RAS* [21], and *PIK3CA* [21]. The reported frequency of BRAF V600E mutation in the largest cohort studied is approximately 58% (46/80) [21], while *RAS* and *PIK3CA* mutations occur at a much lower frequency [21], 18% (3/17) and 13% (7/55), respectively. Rarely, a cytogenetic abnormality involving the balanced chromosomal translocation t(12;15;20)(q11;q24;p13.3) has also been reported [22].

We herein report a unique case of ECD incidentally discovered in a liver explant and bone marrow of a patient with pre-existing HCV hepatitis. Although no mutations in the *BRAF*, *RAS*, and *PIK3CA* genes were identified, novel and potentially significant mutations in the *PDGFRA*, *PTEN* and *HNF1A* genes were detected. These new genomic

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findings expand our understanding of the underlying molecular mechanism of ECD.

2. Clinical summary

A 65-year-old male with hepatitis C diagnosed in 1993, cirrhosis diagnosed in 2002 (outside biopsy not available for review), and frequent ascites underwent liver transplant in 2013. His past medical history was significant for pancytopenia, and work-up showed paraproteinemia, or monoclonal gammopathy of undetermined significance (MGUS), with increased serum κ light chains and a skewed κ:λ ratio of 7:1. However, a bone marrow biopsy performed in early 2012 showed clusters of large foamy histiocytes with no evidence of monotypic plasma cells. Similar histiocytosis was noted in the explant liver one year later, which in combination with bone marrow biopsy findings are characteristic of ECD. The patient then underwent a systemic skeletal examination to rule out bone involvement. Although no clear evidence of osteolytic or osteosclerotic lesions was identified, there was increased heterogeneous uptake in bilateral humeral and femoral diaphyses revealed by fluorodeoxyglucose (FDG) whole body PET scan (Fig. 1A and B) and bone scan (Fig. 1C), findings that are compatible with ECD.

During the two-year's follow-up, the patient underwent a liver needle core biopsy at 6 months after the liver transplant, which showed early recurrent hepatitis C, but no evidence of histiocytosis (data not shown). After anti-hepatitis C therapy, his liver function normalized and no further biopsies have been performed since then. He continued to have mild pancytopenia and mild IgG kappa paraprotein with no evidence of disease progression. Other than early biliary anastomotic strictures requiring stent placement, a resection of an inguinal hernia sac, and a suspicion for pleural effusion on recent imaging studies, the patient has been doing well without specific treatment for ECD.

3. Materials and methods

3.1. Tissue samples

Sections from formalin-fixed, decalcified, paraffin-embedded (FFPE) bone marrow biopsy were stained with hematoxylin and eosin (H&E) and reviewed. Tissue obtained from the liver explant specimen was fixed in 10% buffered formalin for overnight, routinely processed, sectioned and stained with H&E, trichrome, PASD, and reticulin. Special stains for microorganisms, including FITE, GMS, PAS, and Ziehl-Neelsen were performed according to standard procedure.

3.2. Immunohistochemistry

FFPE sections 3–4 μm in thickness from bone marrow biopsy and liver explant were mounted on positively charged glass slides. The immunohistochemistry was carried out according to established protocols using 3,3′-diaminobenzidine detection kit (indirect biotin-avidin system) and an automated immunostainer (Ventana Medical Systems, or Dako autostainer). The following antibodies were used: CD1a (Cell Marque, 1.51 μg/mL), CD68 (Cell Marque, 0.04 μg/mL), CMV (Cell Marque, 0.255 μg/mL), factor XIIIa (Biocare Medical, 250 μg/mL), and S100 (Invitrogen, 0.132 μg/mL). Internal and external controls and irrelevant antibodies in each staining run were acceptable.

3.3. Molecular studies using next generation sequencing (NGS)

Evaluation of mutational hotspots in a panel of 47 clinically relevant genes for solid tumors was performed by NGS using DNA extracted from FFPE liver explant tissue. The genes included in this panel are as follows:

ABL1	*AKT1*	*ALK*	*APC*	*ATM*	*BRAF*
CDH1	*CSF1R*	*CTNNB1*	*EGFR*	*ERBB2*	*ERBB4*
FBXW7	*FGFR1*	*FGFR2*	*FGFR3*	*FLT3*	*GNA11*
GNAQ	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*JAK2*
JAK3	*KDR*	*KIT*	*KRAS*	*MET*	*MLH1*
MPL	*NOTCH1*	*NPM1*	*NRAS*	*PDGFRA*	*PIK3CA*
PTEN	*PTPN11*	*RB1*	*RET*	*SMAD4*	*SMARCB1*
SMO	*SRC*	*STK11*	*TP53*	*VHL*	

Amplicon-based sequencing libraries were created from each specimen using the Illumina TruSeq Amplicon—Cancer Panel Library Prep Kit (Illumina, Inc., San Diego, CA). Libraries were sequenced to a minimum coverage of 500X on a MiSeq instrument (Illumina) using paired 150 base pair reads. A custom bioinformatics analysis pipeline was employed to align the reads to the targeted regions in the genome, call variants, and annotate variants with respect to somatic status and functional predictions. All variants deemed significant were confirmed by Sanger sequencing analysis.

4. Results

4.1. Histopathological findings

The bone marrow biopsy showed clusters and sheets of large cells with abundant foamy cytoplasm in a mildly hypercellular marrow with trilineage hematopoiesis (Fig. 2A). There was no morphological and immunophenotypic (flow cytometry and immunohistochemistry) evidence of plasma cell dyscrasia and cytogenetics revealed normal male karyotype (data not shown).

The liver explant weighed 1777 g and measured 30.8 × 19.5 × 8.5 cm. Macroscopically, the hepatic capsule was red-brown, hemorrhagic, and nodular, typical of a cirrhotic liver as expected. It was also remarkable for white-tan exudative material located at the junction of the left and right lobes and involving the caudate lobe. Microscopically, there were changes consistent with chronic viral hepatitis with moderate activity and advanced bridging fibrosis bordering on cirrhosis (stage 5/6). Yet, similar to the findings in bone marrow, a cardinal feature of the liver was presence of sheets of bland-appearing foamy histiocytes near the capsular surface and in large portal areas associated with fibrosis (Fig. 2B–D). No hepatocellular neoplasms or Michaelis-Guttman bodies were present.

4.2. Immunohistochemistry

The foamy histiocytes in both the liver and bone marrow were strongly positive for CD68 and Factor XIIIa, but negative for CD1a and S100 (Fig. 3A–D), confirming a histiocytic origin that is seen in ECD. No evidence for mycobacterial or fungal micro-organisms was identified by Ziehl-Neelsen, FITE, and GMS special stains. No Michaelis-Guttman bodies were identified on PASD stain to suggest malakoplakia. There was no cytomegalovirus (CMV) detected by immunohistochemistry (data not shown).

4.3. NGS molecular findings

Three potentially significant variants were detected: *PDGFRA* c.2096A>T (p.E699V), *PTEN* c.775C>T (p.H259Y), and *HNF1A* c.938_940delCCC (p.P314del). The *PDGFRA* and *PTEN* mutations are single nucleotide variants resulting in non-synonymous amino acid changes, whereas the *HNF1A* mutation is a deletion of three nucleotides, resulting in an in-frame deletion of a proline residue at amino acid position 314 of 631. Of note, each mutation was detected at a measured allele frequency of approximately 15% (Table 1), sug-

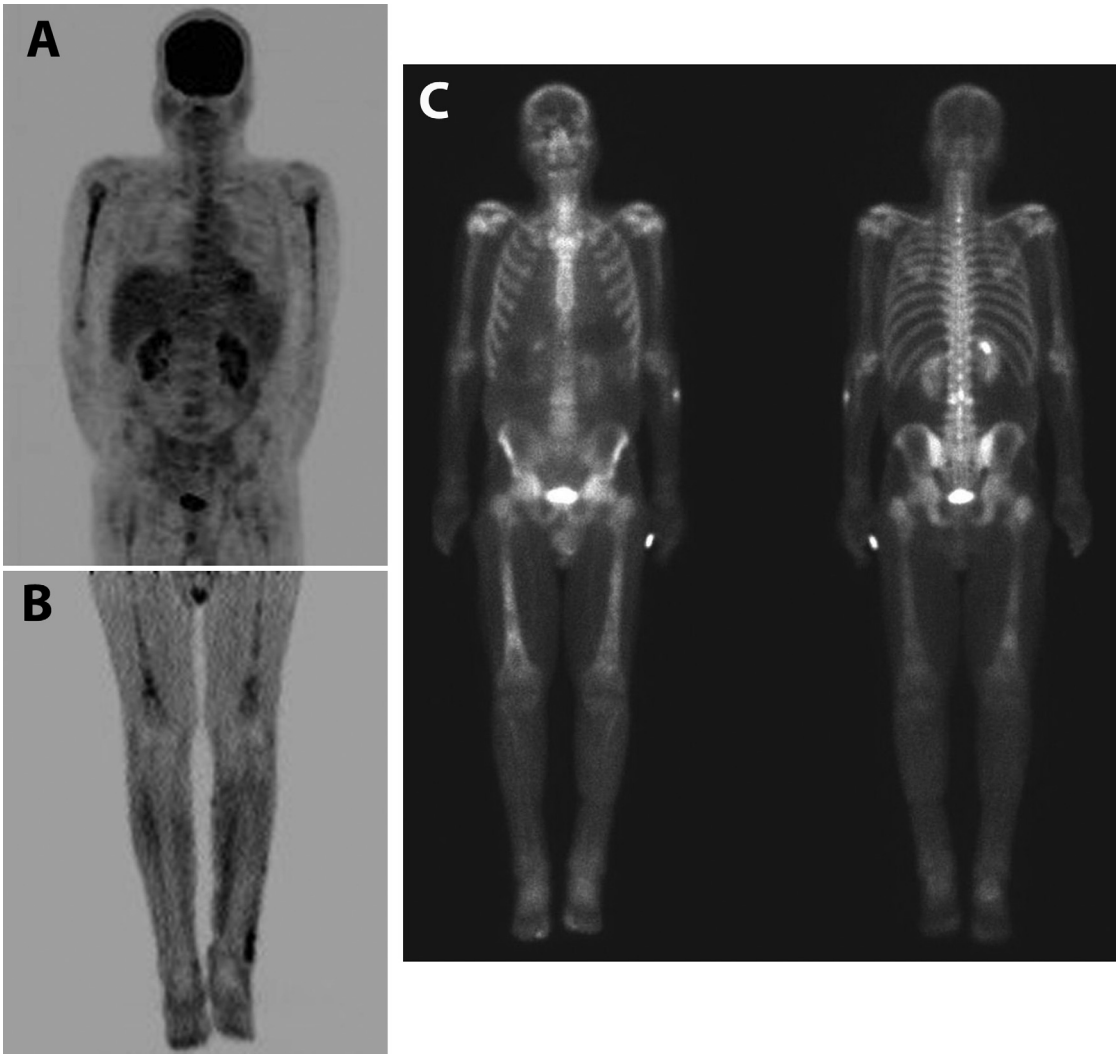

Fig. 1. Imaging findings. On PET scan, increased heterogeneous uptake is present in the bilateral humeral (A) and femoral (B) diaphyses. (C) Whole body bone scan. Anterior (right) and posterior (left) projections, 4 h after 25mCi of Tc-99m MDP (methylene diphosphonate) intravenous injections, show increased uptake in the right distal humerus and both femoral diaphyses and metaphyses.

Table 1
Three potentially significant variants detected (*PDGFRA*, *PTEN*, and *HNF1A*), each at approximately 15% frequency.

GENE NAME	*PDGFRA*	*PTEN*	*HNF1A*
Chromosome position	chr4_55144622	chr10_89717750	chr12_121432190
Reference	A	C	TCCC
Variant	T	T	T
Coding change	c.2096A > T	c.775C > T	c.938_940delCCC
Protein change	p.E699V	p.H259Y	p.P314del

gesting that these likely represent an overall tumor percentage of 30% in the specimen (which is consistent with the histological estimation of tumor volume on the tissue block). Interestingly, the BRAF V600E mutation, which is most frequently associated with ECD, was not detected in our case.

5. Discussion

We report here a unique and interesting case of ECD with the following two features: first, it mainly involves liver, bone marrow and bone; secondly, it possesses novel genomic alterations in *PDGFRA*, *PTEN* and *HNF1A*, which may have potential therapeutic applications in its treatment. To our best knowledge, these genomic mutations have not been previously reported in this disease.

While ECD involves different organ systems and exhibits diverse clinical manifestations, liver involvement is extremely rare. Including the present study, only seven cases of ECD involving the hepatobiliary system have been identified to date [8,23–27]. Interestingly, all seven cases were males with an average age of 47 (21–69) years. Histopathological findings in these seven cases were slightly different: five cases showed mainly portal histiocytosis, one case described extensive hepatic lobular tissue involvement, and one demonstrated bile duct fibrosis with no hepatic parenchyma damage (Table 2). Among these 7 cases, other organ systems were also variably affected, including the bone and bone marrow. Follow-up in 4 cases revealed diverse clinical courses ranging from stable condition to rapid death, similar to other cases of ECD without liver involvement.

The 2008 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues categorizes ECD under “disseminated juvenile xanthogranuloma (JXG)”, as a possible adult form of JXG with bone and lung involvement [28], while the non-JXG family includes “sinus histiocytosis with massive lymphadenopathy” (Rosai-Dorfman disease). Both Rosai-Dorfman disease and JXG/ECD belong to a family of histiocytic disorders, aka non-Langerhans

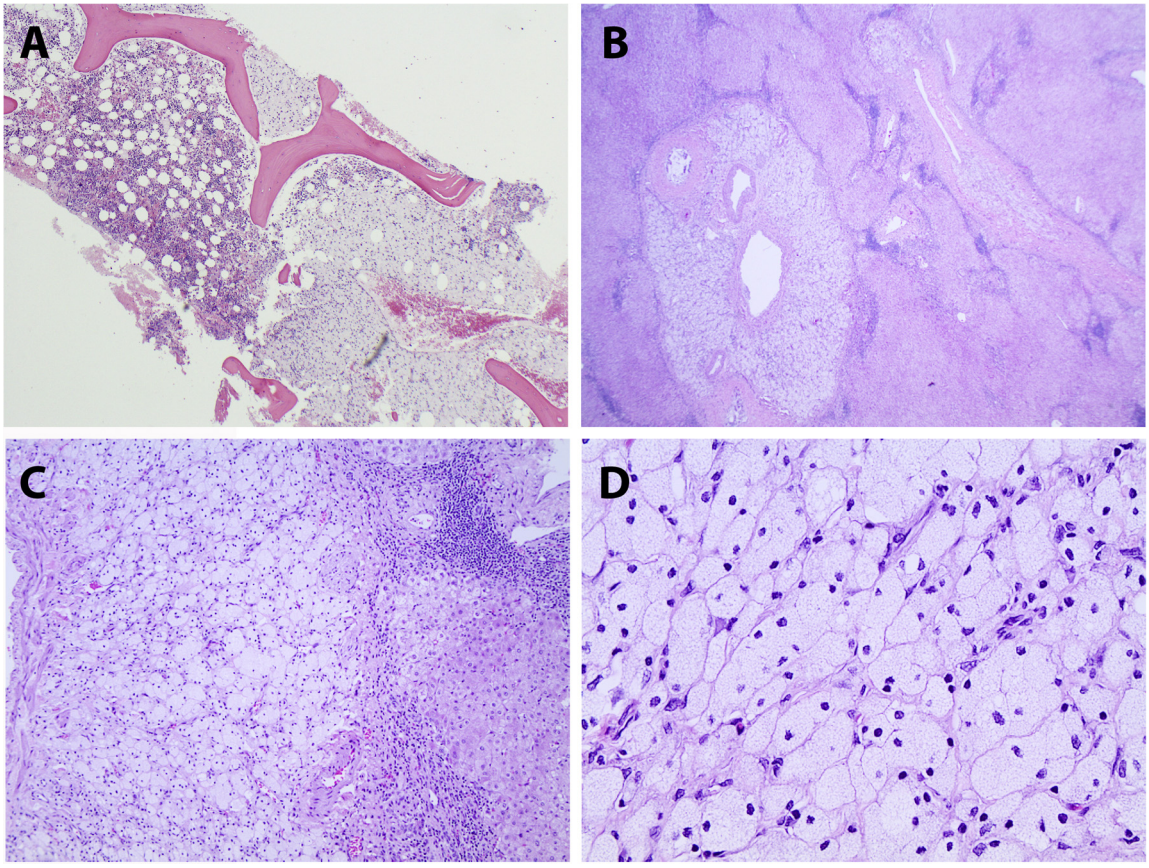

Fig. 2. Histopathologic findings. (A) Bone marrow with clusters of foamy histiocytes (H&E, 20X); (B–D) Liver with abundant foamy histiocytes expanding large portal tract (H&E, 20X, 200X, and 400X, respectively).

Table 2
Summary of ECD cases with hepatobiliary involvement.

Author/Year	Age/Gender	Initial symptoms	Liver manifestation	Other organ systems	Follow-up
Current case	65/M	End stage liver failure	Capsular surface and portal areas with fibrosis and inflammation	Bone/bone marrow	Stable
Tsynman et al. [27]	49/M	Dyspnea, fatigue and ascites	Periportal inflammatory infiltrate and fibrosis	n.a.	n.a.
Pan et al. [8]	69/M	Fever, and gastrointestinal symptoms	Xanthogranulomatous infiltration	Bone, lung, kidney, omentum, small bowel	Died in one month
Gupta et al. [24]	44/M	Fever, dyspnea, limb pain	Histiocytes, fibroblasts, lymphocytes and a few plasma cells	Bone, lung	n.a.
Gundling et al. [23]	50/M	Elevated liver enzymes	Large tumor in liver hilum with bile duct stenosis	Pituitary (1 yr before)	Stable
Ivan et al. [25]	32/M	Motor weakness	Histiocytosis, lymphocytic inflammation, fibrosis, and granulomas	Bone	n.a.
Sandrok et al. [26]	21/M	Progressive bone pain and pericardial effusion	Involved but not specified	Bone, pericardium, pleura, spleen, thyroid, skin, conjunctiva, gingiva, and false vocal cord	Stable

n.a.: Unknown or not reported.

cell histiocytosis (non-LCH) as opposed to LCH. This classification is based upon unique cell origin and immunoprofiles: whereas non-LCH (including ECD) is of CD68+/CD1a- monocyte/macrophage origin, LCH is derived from CD1a+/Langerin+/S100+ dendritic cells. Since both originate from CD34+ hematopoietic stem cells, the distinction between LCH and non-LCH may not always be clear-cut; in fact, both conditions can occur in the same patient [29]. Furthermore, both LCH and ECD conditions are associated with a high prevalence of the BRAF V600E mutation [30,31], suggesting a common pathogenesis for both disease entities [32]. In addition, a recent revised classification from the Working Group of the Histiocyte Society has proposed including LCH, ECD and extra-cutaneous JXG in a single group given the overlapping features [33].

The differential diagnosis of ECD can be very challenging. Infectious etiologies should always be considered and ruled out, as in our case. Involvement in bone and/or bone marrow should also be differentiated from other medical conditions on a case-by-case basis, such as osteomylitiis, Paget's disease, lymphoma, sarcoidosis, and

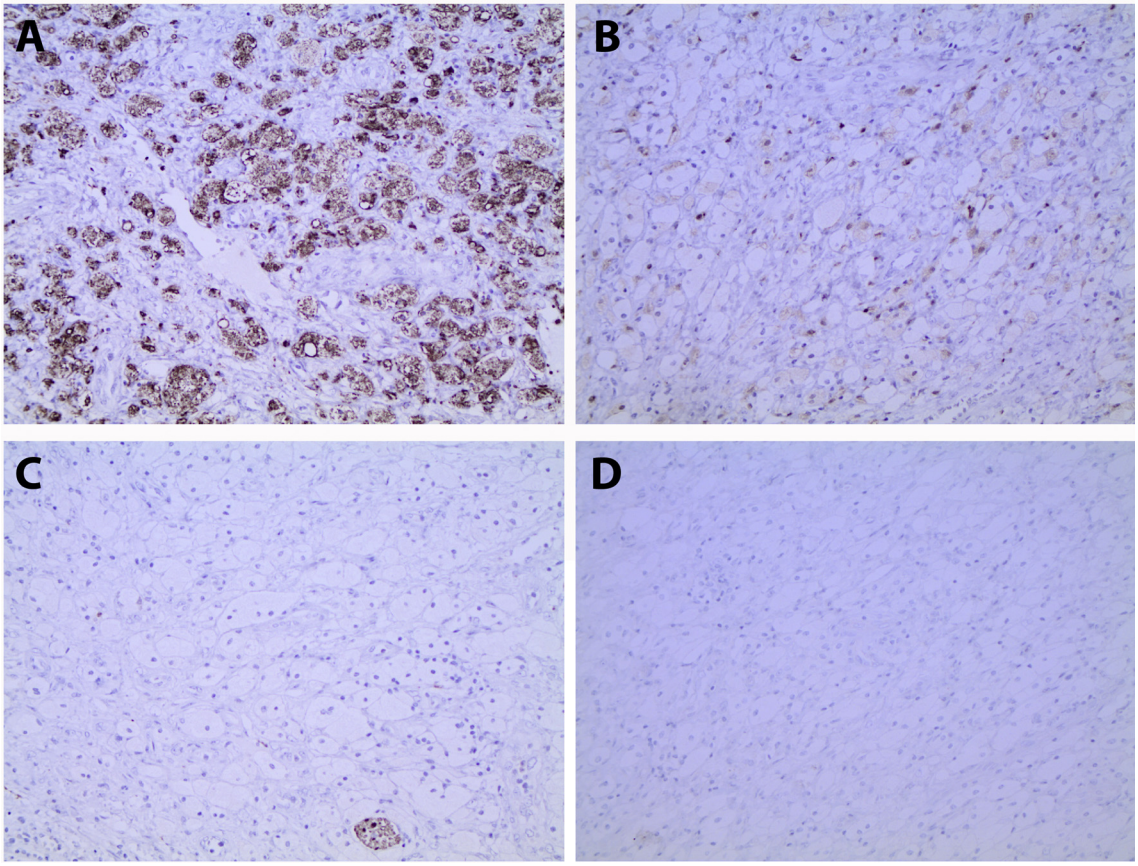

Fig. 3. Immunohistochemical profile of foamy histiocytes. The foamy histiocytes are strongly positive for CD68 (A, 400X) and Factor XIIIa (B, 400X), but negative for S100 (C, 400X) and CD1a (D, 400X).

glycogen or lipid storage disease (Gaucher or Niemann-Pick disease) especially when it involves both the liver and bone marrow. In this situation, a thorough family history and complete understanding of the clinical presentation are important to make the correct diagnosis.

In our case, although no *BRAF*, *RAS*, or *PI3K* mutations were identified, potentially significant mutations in *PDGFRA*, *PTEN*, and *HNF1A* are present. Each of these 3 genes is a known oncogene or tumor suppressor gene. *PDGFRA*, a tyrosine kinase receptor,mutations have been described in patients with gastrointestinal stromal tumors [34] and myeloid/lymphoid malignancies associated with hypereosinophilia [35]. *PTEN*, a tumor suppressor gene, is a negative regulator of the PI3K signaling and mutations of this gene are seen in many neoplastic syndromes [36]. *HNF1A* mutations have been implicated in hepatic adenoma and pancreatic cancer [37]. The significance of these mutations identified in our case is not entirely clear. None of the these mutations have been reported in the Catalog of Somatic Mutations in Cancer (COSMIC) database previously; however, analysis of these variants using the SIFT and PolyPhen-2 functional impact prediction algorithms indicates that each is "damaging" or "potentially damaging" to the encoded protein. Additional work to identify the true functional significance of each will be necessary to more completely elucidate their role, if any, in the pathogenesis of ECD.

Despite the recently identified genetic mutations, the etiology of ECD and the nature of this entity being reactive or neoplastic has long been debated [14,38]. The network of proinflammatory cyto/chemokines responsible for the recruitment and activation of histiocytes into ECD lesions and the presence of oncogenic mutations (such as BRAF V600E) led to the "oncogene-induced senescence (OIS)" hypothesis, where a protective mechanism against oncogenic events is activated by cell cycle arrest and the induction of pro-inflammatory molecules [14,17]. This hypothesis suggests that the inflammatory local and systemic effects in ECD represent an uncontrolled reaction in OIS. On the other hand, some authors suggest that all of the histiocytic disorders including LCH and ECD should be classified as "inflammatory myeloid neoplasms" [38], incorporating both the "inflammatory and neoplastic" features of these entities. How these features relate to the diverse disease process and prognosis are currently not clear.

Therapeutic management is usually recommended for all ECD patients except those with asymptomatic disease [39]. Traditionally, chemotherapy involving cytotoxic drugs and corticosteroids were used until interferon-alpha (IFN-α) became the first-line therapy after its efficacy was first noted in 2005 [40]. With the advent of identifying specific mutations in the *BRAF* gene, targeted therapy with vermurafenib has achieved great success not only in tumors harboring this mutation, but also in LCH and ECD patients [41]. Interestingly, the tyrosine kinase inhibitor Imatinib mesylate has also been successfully used in some patients with histiocytic disorders, even though no mutations in *KIT*, *ABL*, or *PDGFR* have been reported in those cases [42,43]. In that aspect, the PDGFRA E699V, a novel mutation identified in our case, provided the concrete scientific evidence that tyrosine kinase inhibitor can be used in selected cases.

To summarize, we present a unique case of ECD that manifested first in liver and bone marrow with potentially significant mutations in the *PDGFRA*, *PTEN*, and *HNF1A* genes. This case is peculiar and presents a diagnostic challenge as the clinical presentation is non-specific and confounded by pre-existing hepatitis C infection. Awareness of ECD and correlation with clinical presentation is critical to recognize this rare disease entity. Further studies are needed

to evaluate the possible contribution of the newly identified genetic mutations in the etiology of ECD.

References

[1] M. Cives, V. Simone, F.M. Rizzo, F. Dicuonzo, M. Cristallo Lacalamita, G. Ingravallo, F. Silvestris, F. Dammacco, Erdheim-Chester disease: a systematic review, Crit. Rev. Oncol. Hematol. 95 (2015) 1–11.
[2] A.M. Abdelfattah, K. Arnaout, I.A. Tabbara, Erdheim-Chester disease: a comprehensive review, Anticancer Res. 34 (2014) 3257–3261.
[3] R.D. Mazor, M. Manevich-Mazor, Y. Shoenfeld, Erdheim-Chester disease: a comprehensive review of the literature, Orphanet J. Rare Dis. 8 (2013) 137.
[4] C. Campochiaro, A. Tomelleri, G. Cavalli, A. Berti, L. Dagna, Erdheim-Chester disease, Eur. J. Intern. Med. 26 (2015) 223–229.
[5] W.J. Loh, K. Sittampalam, S.C. Tan, M. Chandran, Symptomatic empty sella syndrome: an unusual manifestation of Erdheim-Chester disease, Endocrinol. Diabetes Metab. Case Rep. 2015 (2015) 140122.
[6] K.H. Wittenberg, S.J. Swensen, J.L. Myers, Pulmonary involvement with Erdheim-Chester disease: radiographic and CT findings, AJR Am. J. Roentgenol. 174 (2000) 1327–1331.
[7] J. Haroche, P. Cluzel, D. Toledano, G. Montalescot, D. Touitou, P.A. Grenier, J.C. Piette, Z. Amoura, Images in cardiovascular medicine. Cardiac involvement in Erdheim-Chester disease: magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients, Circulation 119 (2009) e597–598.
[8] A. Pan, T. Doyle, M. Schlup, R. Lubcke, M. Schultz, Unusual manifestation of Erdheim-Chester disease, BMC Gastroenterol. 11 (2011) 77.
[9] K. Loddenkemper, B. Hoyer, C. Loddenkemper, K.G. Hermann, P. Rogalla, G. Forster, F. Buttgereit, F. Hiepe, G.R. Burmester, A case of Erdheim-Chester disease initially mistaken for Ormond's disease. Nature clinical practice, Rheumatology 4 (2008) 50–55.
[10] E.R. Volpicelli, L. Doyle, J.P. Annes, M.F. Murray, E. Jacobsen, G.F. Murphy, A.P. Saavedra, Erdheim-Chester disease presenting with cutaneous involvement: a case report and literature review, J. Cutan. Pathol. 38 (2011) 280–285.
[11] D.A. Yelfimov, D.J. Lightner, M.K. Tollefson, Urologic manifestations of Erdheim-Chester disease, Urology 84 (2014) 218–221.
[12] S.Y. Sheu, R.R. Wenzel, C. Kersting, R. Merten, F. Otterbach, K.W. Schmid, Erdheim-Chester disease: case report with multisystemic manifestations including testes, thyroid, and lymph nodes, and a review of literature, J. Clin. Pathol. 57 (2004) 1225–1228.
[13] E.M. Hoffmann, W. Muller-Forell, S. Pitz, H. Radner, Erdheim-Chester disease: a case report. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle, Ophthalmologie 242 (2004) 803–807.
[14] G. Cavalli, R. Biavasco, B. Borgiani, L. Dagna, Oncogene-induced senescence as a new mechanism of disease: the paradigm of Erdheim-Chester disease, Front. Immunol. 5 (2014) 281.
[15] M. De Filippo, A. Ingegnoli, A. Carloni, E. Verardo, N. Sverzellati, M. Onniboni, A. Corsi, S. Tomassetti, M. Mazzei, L. Volterrani, V. Poletti, M. Zompatori, Erdheim-Chester disease: clinical and radiological findings, La Radiol. Med. 114 (2009) 1319–1329.
[16] A.J. Egan, L.A. Boardman, H.D. Tazelaar, S.J. Swensen, J.R. Jett, S.A. Yousem, J.L. Myers, Erdheim-Chester disease: clinical radiologic, and histopathologic findings in five patients with interstitial lung disease, Am. J. Surg. Pathol. 23 (1999) 17–26.
[17] M.G. Cangi, R. Biavasco, G. Cavalli, G. Grassini, E. Dal-Cin, C. Campochiaro, B. Guglielmi, A. Berti, V. Lampasona, A. von Deimling, M.G. Sabbadini, M. Ferrarini, C. Doglioni, L. Dagna, BRAFV600E-mutation is invariably present and associated to oncogene-induced senescence in Erdheim-Chester disease, Ann. Rheum. Dis. 74 (2015) 1596–1602.
[18] J.F. Emile, F. Charlotte, Z. Amoura, J. Haroche, BRAF mutations in Erdheim-Chester disease, J. Clin. Oncol. 31 (2013) 398.
[19] J. Haroche, F. Charlotte, L. Arnaud, A. von Deimling, Z. Helias-Rodzewicz, B. Hervier, F. Cohen-Aubart, D. Launay, A. Lesot, K. Mokhtari, D. Canioni, L. Galmiche, C. Rose, M. Schmalzing, S. Croockewit, M. Kambouchner, M.C. Copin, S. Fraitag, F. Sahm, N. Brousse, Z. Amoura, J. Donadieu, J.F. Emile, High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses, Blood 120 (2012) 2700–2703.
[20] M.G. Cangi, R. Biavasco, G. Cavalli, G. Grassini, E. Dal-Cin, C. Campochiaro, B. Guglielmi, A. Berti, V. Lampasona, A. von Deimling, M.G. Sabbadini, M. Ferrarini, C. Doglioni, L. Dagna, BRAFV600E-mutation is invariably present and associated to oncogene-induced senescence in Erdheim-Chester disease, Ann. Rheum. Dis. (2014).
[21] J.F. Emile, E.L. Diamond, Z. Helias-Rodzewicz, F. Cohen-Aubart, F. Charlotte, D.M. Hyman, E. Kim, R. Rampal, M. Patel, C. Ganzel, S. Aumann, G. Faucher, C. Le Gall, K. Leroy, M. Colombat, J.E. Kahn, S. Trad, P. Nizard, J. Donadieu, V. Taly, Z. Amoura, O. Abdel-Wahab, J. Haroche, Recurrent RAS and PIK3CA mutations in Erdheim-Chester disease, Blood 124 (2014) 3016–3019.
[22] E.F. Vencio, R.B. Jenkins, J.L. Schiller, T.V. Huynh, D.D. Wenger, C.Y. Inwards, A.M. Oliveira, Clonal cytogenetic abnormalities in Erdheim-Chester disease, Am. J. Surg. Pathol. 31 (2007) 319–321.
[23] F. Gundling, A. Nerlich, W.U. Heitland, W. Schepp, Biliary manifestation of Erdheim-Chester disease mimicking Klatskin's carcinoma, Am. J. Gastroenterol. 102 (2007) 452–454.
[24] A. Gupta, K. Aman, M. Al-Babtain, H. Al-Wazzan, R. Morouf, Multisystem Erdheim-Chester disease; a unique presentation with liver and axial skeletal involvement, Br. J. Haematol. 138 (2007) 280.
[25] D. Ivan, A. Neto, L. Lemos, A. Gupta, Erdhem-Chester disease: a unique presentation with liver involvement and vertebral osteolytic lesions, Arch. Pathol. Lab. Med. 127 (2003) e337–339.
[26] D. Sandrock, M.J. Merino, B.H. Scheffknecht, R.D. Neumann, Scintigraphic findings and follow up in Erdheim-Chester disease, Eur. J. Nucl. Med. 16 (1990) 55–60.
[27] D.N. Tsynman, C. Weaver, S. Taboada, J. Findeis-Hosey, B. Maliakkal, J. Huang, Portal hypertension and ascites secondary to Erdheim Chester disease without intrinsic liver involvement on liver biopsy, Dig. Liver Dis. 45 (2013) 964–965.
[28] S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele, J.W. Vardiman, Disseminated juvenile xanthogranuloma, in: S.H. Swerdlow, International Agency for Research on Cancer, World Health Organization (Eds.), WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed., International Agency for Research on Cancer, Lyon, France, 2008, 439 p.
[29] S.L. Pineles, G.T. Liu, X. Acebes, J. Arruga, S. Nasta, R. Glaser, M. Pramick, F. Fogt, P.L. Roux, R.E. Gausas, Presence of Erdheim-Chester disease and Langerhans cell histiocytosis in the same patient: a report of 2 cases, J. Neuro Ophthalmol. 31 (2011) 217–223.
[30] R. Chakraborty, O.A. Hampton, X. Shen, S.J. Simko, A. Shih, H. Abhyankar, K.P. Lim, K.R. Covington, L. Trevino, N. Dewal, D.M. Muzny, H. Doddapaneni, J. Hu, L. Wang, P.J. Lupo, M.J. Hicks, D.L. Bonilla, K.C. Dwyer, M.L. Berres, P.I. Poulikakos, M. Merad, K.L. McClain, D.A. Wheeler, C.E. Allen, D.W. Parsons, Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis, Blood 124 (2014) 3007–3015.
[31] G. Badalian-Very, J.A. Vergilio, B.A. Degar, L.E. MacConaill, B. Brandner, M.L. Calicchio, F.C. Kuo, A.H. Ligon, K.E. Stevenson, S.M. Kehoe, L.A. Garraway, W.C. Hahn, M. Meyerson, M.D. Fleming, B.J. Rollins, Recurrent BRAF mutations in Langerhans cell histiocytosis, Blood 116 (2010) 1919–1923.
[32] B. Hervier, J. Haroche, L. Arnaud, F. Charlotte, J. Donadieu, A. Neel, F. Lifermann, C. Villabona, B. Graffin, O. Hermine, A. Rigolet, C. Roubille, E. Hachulla, T. Carmoi, M. Bezier, V. Meignin, M. Conrad, L. Marie, E. Kostrzewa, J.M. Michot, S. Barete, V. Taly, K. Cury, J.F. Emile, Z. Amoura, G. French, Histiocytoses study: association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the BRAFV600E mutation, Blood 124 (2014) 1119–1126.
[33] J.F. Emile, O. Abla, S. Fraitag, A. Horne, J. Haroche, J. Donadieu, L. Requena-Caballero, M.B. Jordan, O. Abdel-Wahab, C.E. Allen, F. Charlotte, E.L. Diamond, R.M. Egeler, A. Fischer, J. Gil Herrera, J.I. Henter, F. Janku, M. Merad, J. Picarsic, C. Rodriguez-Galindo, B.J. Rollins, A. Tazi, R. Vassallo, L.M. Weiss, Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages, Blood (2016).
[34] F. Miselli, C. Millefanti, E. Conca, T. Negri, C. Piacenza, M.A. Pierotti, E. Tamborini, S. Pilotti, PDGFRA immunostaining can help in the diagnosis of gastrointestinal stromal tumors, Am. J. Surg. Pathol. 32 (2008) 738–743.
[35] Z. Rudzki, L. Giles, N.C. Cross, M. Lumley, Myeloid neoplasm with rearrangement of PDGFRA, but with no significant eosinophilia: should we broaden the World Health Organization definition of the entity? Br. J. Haematol. 156 (2012) 558.
[36] J.A. Hobert, C. Eng, PTEN hamartoma tumor syndrome: an overview, Genet. Med. 11 (2009) 687–694.
[37] Z. Luo, Y. Li, H. Wang, J. Fleming, M. Li, Y. Kang, R. Zhang, D. Li, Hepatocyte nuclear factor 1A (HNF1A) as a possible tumor suppressor in pancreatic cancer, PLoS One 10 (2015) e0121082.
[38] J. Haroche, F. Cohen-Aubart, F. Charlotte, P. Maksud, P.A. Grenier, P. Cluzel, A. Mathian, J.F. Emile, Z. Amoura, The histiocytosis Erdheim-Chester disease is an inflammatory myeloid neoplasm, Exp. Rev. Clin. Immunol. 11 (2015) 1033–1042.
[39] E.L. Diamond, L. Dagna, D.M. Hyman, G. Cavalli, F. Janku, J. Estrada-Veras, M. Ferrarini, O. Abdel-Wahab, M.L. Heaney, P.J. Scheel, N.K. Feeley, E. Ferrero, K.L. McClain, A. Vaglio, T. Colby, L. Arnaud, J. Haroche, Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease, Blood 124 (2014) 483–492.
[40] F. Braiteh, C. Boxrud, B. Esmaeli, R. Kurzrock, Successful treatment of Erdheim-Chester disease a non-Langerhans-cell histiocytosis, with interferon-alpha, Blood 106 (2005) 2992–2994.
[41] D.M. Hyman, I. Puzanov, V. Subbiah, J.E. Faris, I. Chau, J.Y. Blay, J. Wolf, N.S. Raje, E.L. Diamond, A. Hollebecque, R. Gervais, M.E. Elez-Fernandez, A. Italiano, R.D. Hofheinz, M. Hidalgo, E. Chan, M. Schuler, S.F. Lasserre, M. Makrutzki, F. Sirzen, M.L. Veronese, J. Tabernero, J. Baselga, Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations, N. Engl. J. Med. 373 (2015) 726–736.
[42] J. Utikal, S. Ugurel, H. Kurzen, P. Erben, A. Reiter, A. Hochhaus, T. Nebe, R. Hildenbrand, U. Haberkorn, S. Goerdt, D. Schadendorf, Imatinib as a treatment option for systemic non-Langerhans cell histiocytoses, Arch. Dermatol. 143 (2007) 736–740.
[43] J. Haroche, Z. Amoura, F. Charlotte, J. Salvatierra, B. Wechsler, C. Graux, N. Brousse, J.C. Piette, Imatinib mesylate for platelet-derived growth factor receptor-beta-positive Erdheim-Chester histiocytosis, Blood 111 (2008) 5413–5415.