Quiz

Correct answer to the quiz. Check your diagnosis

Puzzle histiocytosis (solitary mononuclear xanthogranuloma with LCH component). A case report*

Katarzyna Woszczyna-Mleczko[1], Artur Kowalik[2,3], Agnieszka Harazin-Lechowska[1], Piotr Bobkiewicz[4], Andrzej Marszałek[5], Janusz Ryś[1]

[1]Department of Tumour Pathology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Krakow Branch, Poland
[2]Department of Molecular Diagnostics, Holycross Cancer Center, Kielce, Poland
[3]Department of Surgery and Surgical Nursing with the Scientific Research Laboratory, The Faculty of Health Sciences of the Jan Kochanowski University in Kielce, Poland
[4]Pathomorphological Lab AlabPlus, Warsaw, Poland
[5]Department of Tumour Pathology and Prophylaxis, Poznan University of Medical Sciences and Geater Poland Oncology Center, Poznan, Poland

We report a case of 40-year-old Caucasian man presented with an asymptomatic nodule localized on his arm. The puzzle histiocytosis composed of juvenile xanthogranuloma and Langerhans cell histiocytosis was diagnosed. The results of immunohistochemical studies confirm the dual character of histological texture of the lesion.

Key words: Langerhans cell histiocytosis, xanthogranuloma, immunohistochemistry.

Introduction

Xanthogranuloma (XG) and Langerhans cell histiocytosis (LCH) both belong to the histiocytosis group of disorders, and are thought to originate from a common stem cell precursor [1]. What is more a rare cases presenting the overlapping features of LCH and juvenile xanthogranuloma (JXG) have been reported [2, 3, 4]. We describe an additional case of cutaneous lesion with the coexistence of both LCH and XG texture.

Case report

An otherwise healthy, 40-year old Caucasian man presented with a 2-year history of a slow-growing polypoid tumor of the right arm. He had no symptom of fever, malaise or weight loss. Physical examination revealed no sign of lymph nodes enlargement.

A macroscopic examination revealed white-blue skin nodule on the one-third lower part of the right arm, measuring 1 × 1.5 cm. The lesion was excised completely. The patient has been followed up for 20-months without recurrence.

Material and methods

The material was derived from consultation archive. The specimen was fixed in formalin and embedded in paraffin for routine hematoxylin and eosin stain. Immunohistochemical studies included CD68, CD163, Factor XIIIa, CD1a, S-100 protein, Langerin, smooth muscle actin, HMB45, melan A,

*This case was presented during the course titled Dermatopathology Update in benign, borderline and malignant melanocytic lesion and adnexal tumors, Poznan 2016.

Table I. Immunohistochemical reagents

Antibody	Clone	Source	Dilution	Retrival
CD68	514H12	NOVOCASTRA	1 : 80	EDTA BUF.
CD163	MRQ-26	CELL MARQUE	1 : 30	CITRATE BUF.[1]
Factor XIIIa	AC-1A1	NEO MARKERS LAB VISION	1 : 50	None
S-100 protein	NCL-S100p	NOVOCASTRA	1 : 600	TRYPSIN 15'
Langerin	12D6	CELL MARQUE	RTU	CITRATE BUF.[2]
SMA	OCSM-1	NOVOCASTRA	1 : 50	None
HMB45	HMB-45	CELL MARQUE	1 : 200	CITRATE BUF.[1]
Melan A	A103	NOVOCASTRA	1 : 25	CITRATE BUF.[1]
CK (AE1/AE3)	313M-16	CELL MARQUE	1 : 100	CITRATE BUF.[1]
CD20	L26	CELL MARQUE	1 : 200	CITRATE BUF.[2]
CD34	QBEnd10	CELL MARQUE	1 : 50	CITRATE BUF.[1]
CD31	1A10	NEO MARKERS	1 : 50	CITRATE BUF.[1]
BRAF V600E	VE1	VENTANA	RTU	Benchmark Ultra

CITRATE BUF. [1] – citrate buffer, pH = 6.0, microvave oven 600 W 2 × 10', CITRATE BUF. [2] – citrate buffer, pH = 6.0, waterbath 40', EDTA BUF. – EDTA buffer, pH = 8,0, microvave oven 600 W, 2 × 10', RTU – ready to use

cytokeratins, CD20, CD34, CD31 and anti-BRAF antibody. The details of immunohistochemical reagents are depicted in Table I. Genotyping of BRAF p.V600E (c.1799T>A) was performed using qPCR and Sanger sequencing as described previously [5, 6]. Briefly, the tumor tissue on the unstained slides was deparaffinized and transferred from the area selected by a pathologist to a tube for DNA isolation using the Maxwell® 16 FFPE Plus LEV DNA Purification Kit according to the manufacturer's instructions (Promega, USA). We amplified a segment of exon 15 of BRAF 224 bp in length containing codon 600 using the following PCR primers: BRAFek15f (5'-TCATAATGCTTGCTCTGATAGGA-3') and BRAFek15r (5'-GGCCAAAAATTTAATCAGTGGA-3'). A qPCR assay targeting 68 bp of BRAF exon 15 was performed using Rotor-Gene Q (Qiagen, Syngen-Biotech, Poland) with the following primers: forward 5' agacctcacagtaaaaataggtgattttgg 3' and reverse 5' gatgggacccactccatcg 3'. A BRAF mutant-specific probe (6FAM- CTACAGAGAAATC -MG-BNFQ) and BRAF-WT allele-specific probe (VIC- CTACAGTGAAATC -MGB-NFQ) were used.

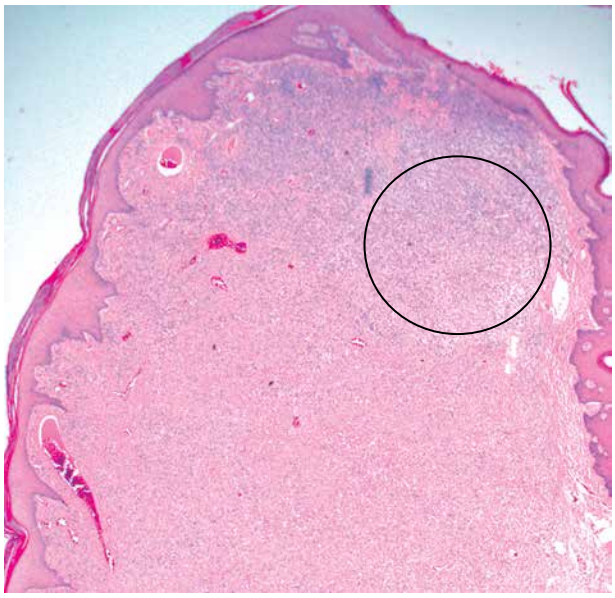

Fig. 1. Cutaneous solitary mononuclear xanthogranuloma with LCH component. The low-power view of the lesion (LCH component marked by circle) HE, low magnification

Morphological characteristics of tumor

Macroscopically as well as on the lower magnification the polypoid tumor was confined to the skin (Fig. 1). The main histological components of the tumor consisted of the mixture of short spindle cells producing collagen fibers, lymphocytes, plasma cells, scattered eosinophils and histiocytoid cells (Figs. 2-3). The histiocytoid cells were characterized by oval, folded nuclei with fine chromatin, inconspicuous nucleoli and thin nuclear membrane. Some of them presented longitudinal nuclear grooves (Fig. 4). The vast majority of tumor cells lacked nuclear atypia, however, a few cells with atypia/pseudoatypia were noticed.

The additional component of the histological texture was a well circumscribed area (Fig. 1 appointed fragment) of mononucleated epithelioid cells characterized by coffee bean- or kidney-shaped nuclei and moderate amount of clear or eosinophilic cytoplasm (Fig. 5). The border between two components of neoplasm was sharp (Fig. 6).

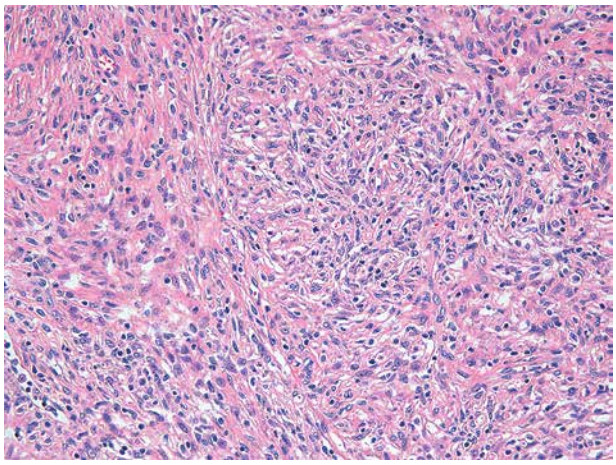

Fig. 2. Histological texture of xanthogranulomatous component of the lesion which consists of the mixture of spindle cells, lymphocytes, plasmocytes, histiocytoid cells and scattered eosinophils HE

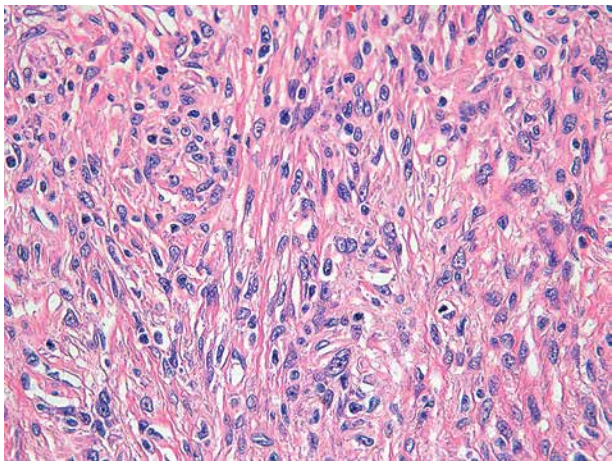

Fig. 3. Histological texture of xanthogranulomatous component of the lesion. HE, higher magnification)

Additionally, these two components of the lesion differed from each other immunohistochemically. The cells of both components stained with antibody against CD68, however the histiocytoid cells were positive for CD68, CD163, factor XIIIa and negative for CD1a, S-100 protein, Langerin, smooth muscle actin, HMB45, cytokeratins, CD20, CD34 and CD31. Contrary to above-mentioned histiocytioid cells, the mononucleated epithelioid cells were immunoreactive for CD1a, S100, Langerin and negative for CD20, CD31, CD34, CD163, SMA, HMB-45, CK, CD163, FXIIIa (Fig. 7). The results of immunohistochemical studies are depicted in the Table II.

The immunohistochemical and molecular tests for *BRAF* (V600E) mutation gave negative results. We did not find BRAF p.V600E (c.1799T>A) mutation in DNA isolated from both components.

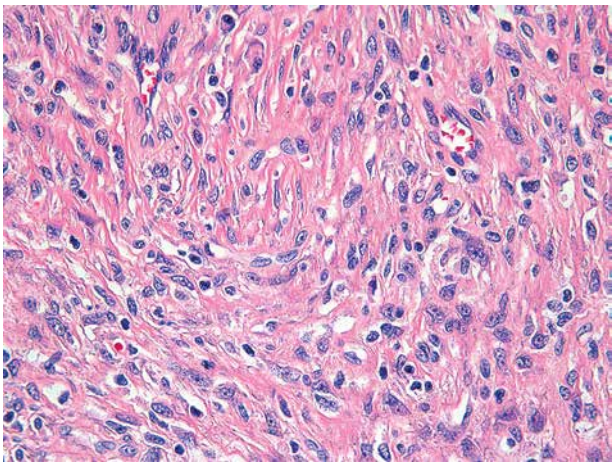

Fig. 4. Histological texture of xanthogranulomatous component of the lesion. Histiocytoid cells characterized by nuclei with longitudinal grooves. HE, high magnification

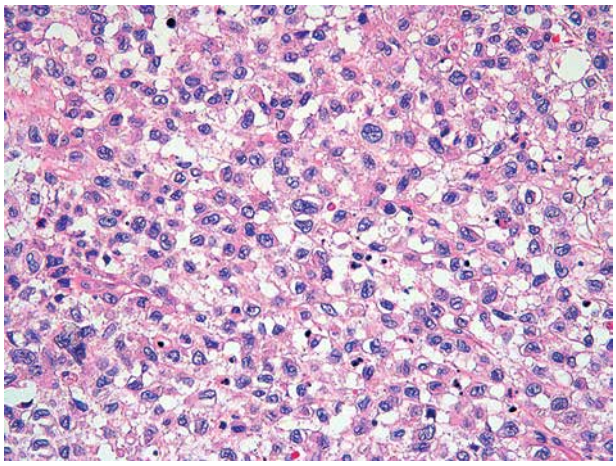

Fig. 5. Histological picture of Langerhans cell component of the lesion built of clear epithelioid cells with coffee-bean- or kidney-shaped nuclei. HE, high magnification

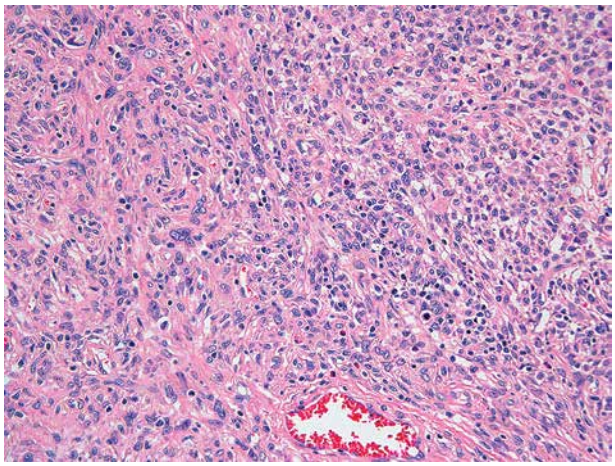

Fig. 6. Histological border between two components of the lesion HE, low magnification

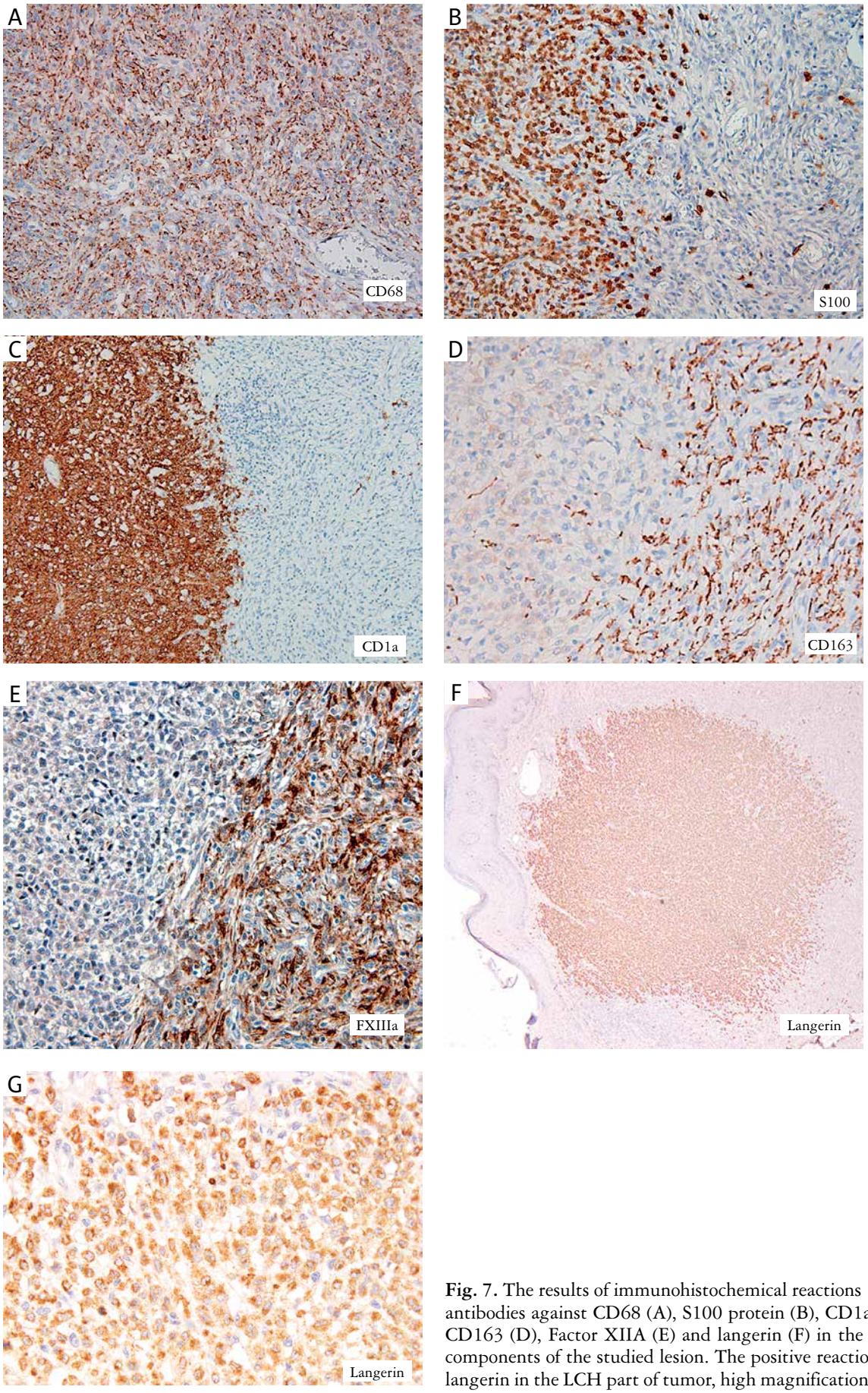

Fig. 7. The results of immunohistochemical reactions with antibodies against CD68 (A), S100 protein (B), CD1a (C), CD163 (D), Factor XIIA (E) and langerin (F) in the both components of the studied lesion. The positive reaction for langerin in the LCH part of tumor, high magnification (G)s

Based on histopathologic and immunohistochemical findings, the puzzle tumor composed of solitary mononuclear xanthogranuloma with additional component of LCH texture was diagnosed.

Discussion

The histiocytoses are rare disorders characterized by the accumulation of cells thought to be derived from dendritic cells (DCs) or macrophages. The revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages consists of 5 categories of diseases:

- Langerhans-related (L-group), which includes LCH and Erdheim-Chester disease,
- cutaneous and mucocutaneous (C-group including JXG),
- malignant histiocytoses (M-group),
- Rosai-Dorfman disease (R-group),
- hemophagocytic lymphohistiocytosis and macrophage activation syndrome (H-group) [1].

Langerhans cell histiocytosis is a localized, multifocal, or disseminated condition characterized by often clonal accumulation of Langerhans-like cells that express CD1a, langerin (CD207), S-100 protein, and Birbeck granules by ultrastructural examination [7] (Table III). The diagnosis of LCH is based on clinical and radiological findings in combination with histopathological analyses identifying tissue infiltration by histiocytes with ultrastructural or immunophenotypic characteristics of LCs. Skin may be the only site of Langerhans cell disease, or it may be part of more widespread involvement. LCH may affect any organ of the body, but those more frequently affected in children are the bones (80% of cases), skin (33%), and the pituitary gland (25%) [1]. The proliferating Langerhans cells have abundant, often vacuolated cytoplasm and vesicular nuclei containing linear grooves or folds. The presence of Birbeck granules in the cytoplasm is characteristic. BRAF V600E mutations were found in 38% to 57% of LCH cases. MAP2K1 mutation is another known mutation [9].

Table II. The immunohistochemical characteristics of the main components of the lesion

Antigen	Spindle cells	Langerhans cells
CD68	(+)	(+)
CD1a	(–)	(+)
S100	(–)	(+)
Langerin (CD207)	(–)	(+)
SMA	(–)	(–)
CD31	(–)	(–)
CD34	(–)	(–)
CD4/CD8	(–)	(–)
CD20	(–)	(–)
HMB45/Melan A	(–)	(–)
FXIIIa	(+)	(–)
CD163	(+)	(–)
Collagen (Masson's trichome)	(+)	(–)

Table III. The immunohistochemical profile of the lesions, which are considered in the differential diagnosis of both xanthogranuloma and Langerhans cell histiocytoma

Antigen	LCH	ICH	RDD	ECD	JXG	Reticul	BFH
CD68	(+)	(+)	(+)	(+)	(+)	(+)	(–)
CD1a	(+)	(+)	(–)	(–)	(–)	(–)	(–)
CD207 Langerin	(+)	(–)	(–)	(–)	(–)	(–)	(–)
S100	(+)	(–/+)	(+)	(–/+)	(–)	(–/+)	(–)*
SMA	(–)	(–)	(–)	(–)	(–)	(–)	(+) foc
CD31	(–)	(–)	(–)	(–)	(+/–)	(–/+)	(–)
CD34	(–)	(–)	(–)	(–)	(–)	(–)	(–)
CD4	(–)	(–)	(–)	(–)	(+)	(–)	(–)
FXIIIa	(–)	n.d.	(–)	(+)	(+)	(+)	(–/+)
CD163	(–)	n.d.	(+)	(+)	(+)	(+)	(–)
BRAF V600E	(+)	(–)	(–)	(+)	(–)	(–)	(–)
ME Birbek gr	(+)	(–)	(–)	(–)	(–)	(–)	(–)

LCH – Langerhans cell histiocytosis; ICH – intermediate cell histiocytosis; RDD – Rosai-Dorfman disease; ECD – Erdheim-Chester disease; JXG – juvenile xanthogranuloma; RETICUL – reticulohistiocytoma; BFH – benign fibrous histiocytoma

Juvenile xanthogranuloma is a benign dermal histiocytic disorder that occurs as single or multiple yellowish nodules that usually involve primarily the head and neck, trunk, or upper extremities. Histologically, there is a nodular, poorly demarcated dense infiltrate of small histiocytes involving the dermis and sometimes the upper subcutis as well. Rarely, deep extension into skeletal muscle is present. Early lesions consist of monomorphic, histiocytic infiltrate. Mature lesions contain foamy histiocytes, Touton giant cells and foreign body giant cells, as well as mixed cellular infiltrate of lymphocytes, macrophages and eosinophils. Fibrosis may be prominent. Mitotic figures are rare [7, 8].

In our opinion the histological picture of presented lesion is built of the texture typical for both above mentioned categories of histiocytic proliferations (xanthogranuloma & Langerhans cell histiocytosis). What is more, the immunohistochemical profile of the both components confirmed the diagnosis of puzzle lesion and allows to exclude the selected lesions which are usually considered in the differential diagnosis of xanthogranuloma and LCH histiocytosis (Table III).

There are very few reports in literarure describing the two different types of histiocytoses coexisting in the same patient. Yu *et al*. reported the case of a 15-month-old boy with a histiocytosis of the skin with hybrid features of JXG and LCH [3]. Martín *et al*. described the case of multiple cutaneous lesions in a 10-year-old boy, in whom the coexistence of both LCH and JXG cell populations was found in every single lesion [4]. Shani-Adir *et al*. reported the case of a 2-years-old boy who referred with both JXG of the skin and LCH with bone involvement [2].

In addition, in the literature JXG was described as a sequel to LCH treated with chemotherapy [10].

The authors declare no conflict of interest.

References

1. 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.
2. Shani-Adir A, Chou P, Morgan E, et al. A Child with both Langerhans and non-Langerhans cell histiocytosis. Pediatr Dermatol 2002; 19: 419-422.
3. Yu H, Kong J, Gu Y, et al. A child with coexistent juvenile xanthogranuloma and Langerhans cell histiocytosis. J Am Acad Dermatol 2010; 62: 329-332.
4. Martín JM, Jordá E, Martín-Gorgojo A, et al. Histiocytosis with mixed cell populations. J Cutan Pathol 2016; 43: 456-460.
5. Lasota J, Kowalik A, Wasag B, et al. Detection of the BRAF V600E mutation in colon carcinoma: critical evaluation of the imunohistochemical approach. Am J Surg Pathol 2014; 38: 1235-1241.
6. Walczyk A, Kowalska A, Kowalik A, et al. The BRAF(V600E) mutation in papillary thyroid microcarcinoma: does the mutation have an impact on clinical outcome? Clin Endocrinol (Oxf) 2014; 80: 899-904.
7. Jaffe ES. Hematopathology. Saunders, Elsevier, Philadelphia 2011.
8. Weedon D, Strutton G, Rubin AI, Weedon D Weedon's skin pathology. Churchill Livingstone, Elsevier, Edinburgh 2010
9. Brown NA, Furtado LV, Betz BL. High prevalence of somatic MAP2K1 mutations in BRAF V600E–negative Langerhans cell histiocytosis. Blood 2014; 124: 1655-1658.
10. Strehl JD, Stachel KD, Hartmann A, Agaimy A. Juvenile xanthogranuloma developing after treatment of Langerhans cell histiocytosis: case report and literature review. Int J Clin Exp Pathol 2012; 5: 720-725.

Address for correspondence

Katarzyna Woszczyna-Mleczko
Department of Tumour Pathology
Maria Sklodowska-Curie Memorial Cancer Centre
and Institute of Oncology
Krakow Branch, Poland
e-mail: kasia.woszczyna@gmail.com