Original Article

Effective treatment of progressive nodular histiocytosis by intermediate-dose cytarabine: a case report and literature review

Ji-Nuo Wang¹, Yu Qiu¹, Jian Sun², Na Niu³, Yang Jiao⁴, Tie-Nan Zhu¹, Jian Li¹, Dao-Bin Zhou¹, Xin-Xin Cao¹

Departments of ¹Hematology, ²Pathology, ³Nuclear Medicine, ⁴General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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Abstract: Background: Progressive nodular histiocytosis (PNH) is a rare, clinically distinct non-Langerhans cell histiocytic neoplasm affecting the skin and mucous membranes with no signs of spontaneous regression of the lesions. Patients typically have hundreds of lesions of superficial xanthomatous papules to nodules and deep larger fibrous nodules, which can be life-threatening if laryngeal mucosa was involved. So far, few cases of PNH have been reported and no effective treatment has been shown to reverse the progressive clinical course. Case presentation: Here we describe a case of PNH presenting as diffuse, progressively enlarging papules, nodules and even leonine appearance in a young woman. The diagnosis was confirmed by histological and immunohistochemical findings. Next-generation sequencing (NGS) showed identical missense mutation in *XIAP*^{P404C} and in-frame deletion in *MAPK1*^{A2[6>5]}. Since ERK inhibitor has not been on the market yet, the patient received chemotherapy instead. Traditional chemotherapy with intermediate-dose of cytarabine (500 mg/m² cytarabine by 3-hour infusion every 12 hours for 3 days every 5 weeks) achieved favorable therapeutic effect as confirmed by clinical symptoms and PET/CT imaging. Conclusions: PNH is a rare, proliferative disorder with disfiguring lesions and deteriorative quality of life. Mutations in *MAPK1*, *XIAP* may play crucial roles in the pathogenesis of PNH. Intermediate-dose cytarabine can be considered as a promising treatment option for PNH patients.

Keywords: Progressive nodular histiocytosis (PNH), non-Langerhans cell histiocytosis (non-LCH), next-generation sequencing, cytarabine

Introduction

Progressive nodular histiocytosis (PNH), first described in 1978 by Taunton et al. [1], is a rare non-Langerhans cell histiocytic neoplasm of unknown cause manifesting as widespread xanthomatous lesions with no spontaneous remission. The clinical presentation of PNH usually consists of yellow-brown or yellow-pink superficial papules or deep nodules ranging from 0.5 to 5 cm in size. Facial involvement is a prominent feature and may cause a leonine appearance. Meanwhile, lesions may coalesce on the eyelids leading to ectropion [2]. While PNH may involve mucous membranes such as in the oral cavity, larynx and conjunctiva, flexural areas and joints are usually spared [3]. To date, few PNH cases have been reported, and even fewer reports have mentioned the treat-

ment. Surgical resection of specific nodules seems to be the only effective therapeutic option, but recurrences were common [4]. Herein, we report the successful treatment of a patient with refractory, disseminated PNH by intermediate-dose cytarabine. This case highlights the identical genetic pathogenesis of PNH, as well as the potential therapeutic effect of cytarabine for histiocytosis.

Case presentation

A 22-year-old woman was referred to our hematology clinic with a 6-year history of papules and nodules appearing throughout the skin. Physical examination revealed reddish-brown papules and nodules involving the face, trunk and extremities (**Figure 1A**). The chest, flexural areas, palms and joints were spared. The nod-

Figure 1. Facial and body characteristic lesions before and after treatment. Reddish-brown papules, nodules and tumors on the face (A) when the patient first came to our clinic; Four years later, she developed leonine appearance (B) and nodules in her body became larger and denser (D). After six courses of cytarabine, Skin lesions throughout her body became soft and smaller (C), especially for feet (E).

ules were perfectly delimited by healthy skin and were mostly mounted on the skin. The conjunctival mucosa was also affected by superficial yellowish papules. Her past medical history was insignificant, and there was no family history of note. Basic laboratory findings were generally within normal limits. Histopathological examination of multiple nodular lesions revealed subcutis and focal skeletal muscle infiltrate, which extended deeply into the reticular dermis and was composed of histiocytes, spindled cells within fibrous matrix and Touton giant cells (**Figure 2A**). Immunohistochemical staining showed that the nodular tissue was positive for CD68 (**Figure 2B**) and S-100 but negative for CD1a (**Figure 2C**). Based on clinical manifestations and pathological findings, a diagnosis of non-Langerhans cell histiocytosis was made. Despite several courses of systemic chemotherapy including cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone, her lesions gradually increased in

size. The patient was disappointed and refused further treatment.

Four years later, she came to our clinic again. Those lesions on the face tended to be grouped, converging around the nasal root, forehead and palpebral areas, resulting in the characteristic leonine face (**Figure 1B**), and the nodules on her body became larger and denser (**Figure 1D**). ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) demonstrated an increased uptake in the cutaneous lesions throughout the body (**Figure 3A**). Rebiopsy showed the same histopathological findings. Based on the two different disseminated skin lesions, histology and progressive course, PNH was diagnosed. We performed next-generation sequencing (NGS) on this patient's nodule tissue and peripheral blood (**Supplementary Table 1**). The results showed activating missense mutation in $\text{XIAP}^{\text{Y404C}}$, in-frame deletion in $\text{MAPK1}^{\text{A2[6>5]}}$, as

Figure 2. Histology of nodular lesion (A) showing diffuse infiltrate of foamy macrophages and multiple Touton giant cells (hematoxylin and eosin stain; original magnification $\times 200$). Immunohistochemistry showing (B) diffuse strong staining for CD68 (DAB stain; $\times 200$), and (C) negative staining for CD1a (DAB stain; $\times 200$).

Figure 3. Pre-treat and post-treat PET-CT imaging. A. Initial ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT scan showed diffused high uptake sites spreading over the skin. B. Repeated ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT showed that the number and uptake of cutaneous nodules were significantly decreased after six courses of cytarabine.

well as germline missense mutation in $\text{CSF3R}^{\text{H54D}}$. However, no mutation or translocation was found in the PI3K-AKT pathway or mTOR pathway.

Since MEK inhibitor has not been on the Chinese market yet, the patient was treated with 500 mg/m^2 cytarabine by 3-hour infusion every 12 hours for 3 days every 5 weeks after signing informed consent. Skin lesions throughout her body became soft and smaller (**Figure 1C, 1E**). Repeated PET/CT scans after six courses of cytarabine showed that the number and uptake of those hypermetabolic lesions were dramatically decreased, especially in the feet (**Figure 3B**). So far, the patient has received seven courses of intermediate-dose cytarabine, and no major adverse events occurred except for transient and

manageable grade 4 myelosuppression without severe infection or hemorrhage. The patient witnessed the decrease of nodules all over her body and was brave enough to go outside and get involved in social activities.

Discussion

PNH is a distinct, unusual variant of cutaneous non-Langerhans cell histiocytosis belonging to the “C” group (cutaneous and mucocutaneous histiocytoses) [5] and it affects the skin and mucous membranes without visceral involvement. To date, only a handful of PNH cases have been reported since the first description in 1978. In order to better understand this rare disease, we reviewed the literature for all the PNH cases, analyzed the data, and depicted the basic clinical characteristics, histopathology, treatment options, and outcome of the disease (Table 1).

The diagnosis of PNH relies heavily on progressive clinical features and pathological results. Typically, patients may progressively develop hundreds of two distinct types of lesions: superficial xanthomatous papules to nodules of 2 to 10 mm in diameter and deep larger fibrous nodules [5, 6]. These lesions are widely and randomly distributed on different sites throughout the body, while the flexural areas and joints are usually spared [3]. Facial involvement is a prominent feature and may cause a leonine appearance, and eyelid, conjunctival, oral, or laryngeal lesions may also occur, which can be life-threatening sometimes due to airway obstruction [2, 5, 7]. The widespread skin nodules and leonine face appearance are problematic for patients especially for a young girl, and will seriously affect the quality of life, impair social interactions, even lead to suicidal tendencies.

Although PNH is commonly localized to skin and/or mucosal surfaces, various associated conditions have been reported, including a male with chronic myeloid leukemia and metabolic disorders [12], a woman with thrombocytopenia and angiofibroma [15] and a 9-year-old girl with a hypothalamic tumor [13]. Additionally, there have been reports of microcytic anemia due to massive iron deposition in the nodules [18].

To our knowledge, this is the first study worldwide to perform next-generation sequencing on

a PNH patient. Those recurrent, activating mutations and fusions that are commonly found in histiocytic neoplasms, such as *BRAF*^{V600E}, *ARAF*, *MAP2K1*, *NRAS*, *KRAS*, *PIK3CA* mutations [26], were not present in our patient. However, germline mutation in *CSF3R* and somatic mutations in *XIAP* and *MAPK1* were found. *XIAP* gene mutations have been identified in some people with X-linked lymphoproliferative disease (XLP). In 2018, Guo et al. reported a boy with *XIAP* mutation manifesting as Langerhans cell histiocytosis complicated with hemophagocytic lymphohistiocytosis [27]. *MAPK1* mutation has been widely recognized in many hematologic malignancies and histiocytosis, like acute myeloid leukemia, Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD). Activating *MAPK1* mutation plays an essential role in RAS-RAF-MEK-ERK cell signaling pathway and is sensitive to ERK inhibition, while resistant to *BRAF* or MEK inhibitors [28]. Mutations in *CSF3R* occur in the majority of patients with chronic neutrophilic leukemia and rarely in patients with acute myeloid leukemia [29]. Recently, Spicciarich et al. discovered a germline mutation in *CSF3R*^{N610H}, which reduces N-glycosylation and exerts potent oncogenic effects in leukemia [30].

Treatment of PNH is difficult. No consensus treatment for PNH exists, and treatment outcomes are often disappointing. Early diagnosis and surgical excision may be an option, but recurrence is common [2-4]. Carbon dioxide laser was also occasionally applied to ablate skin nodules [9, 12, 16]. Traditional chemotherapies including prednisolone, vincristine, and cyclophosphamide have been indicated to be unsuccessful in the literature and in this patient reported [16]. Oral low-dose methotrexate (MTX, 15 mg once/week) was also attempted, but a new flare of PNH lesions occurred after discontinuation of the therapy [24]. *BRAF*, *MEK* and *mTOR* inhibitors have been shown to exert great efficiency in histiocytosis like LCH and ECD. Based on the patient's NGS result, ERK inhibitors could be chosen as the first-line therapy. However, no ERK inhibitors were available on the market. Recently, more evidence has shown that cytarabine is an important drug for the treatment of histiocytosis, including LCH [31, 32] and non-LCH, such as ECD in our previous report [33]. As seen in this case, the patient achieved clinical improvement after six

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Table 1. Characteristics of published PNH cases from 1978 to 2019

Case No.	Year	Age/Sex	Special clinical features	Systematic disease	Histopathology	Treatment	Outcome
1	1978 [1]	9/F	Mucosal involvement; Ocular involvement	Anemia	CD68 (+) S-100 (-)	N/A	N/A
2	1981 [8]	29/M	Spontaneous regression	No	Factor XIIIa (+) Vimentin (+) CD68 (+)	N/A	N/A
3	1993 [9]	60/M	Facial involvement	No	lysozyme (+) a-antitrypsin (+) S-100 (-)	Systemic steroids and antihistamines	No response
4	1995 [10]	62/F	NA	No	Factor XIIIa (+) Vimentin (+) CD68 (+)	N/A	Eighteen months follow-up
5	1995 [10]	52/M	NA	No	Factor XIIIa (+) Vimentin (+) CD68 (+)	N/A	Five years follow-up
6	2000 [11]	25/M	Facial involvement	No	CD68 (+) CD15 (+) S-100 (-) CD1a (-)	Systemic steroids and cyclophosphamide (150mg/d)	No response
7	2000 [12]	57/M	Facial involvement→Ectropion	Chronic myeloid leukemia, hepatosplenomegaly, hypothyroidism, hyperuricemia and hypocholesterolemia	Factor XIIIa (+) CD68 (+) S-100 (-)	Carbon dioxide laser	Recurrence
8	2002 [13]	13/F	Spontaneous regression	Hypothalamic tumor	CD68 (+) S-100 (-) CD1a (-)	Growth hormone releasing hormone agonist and growth hormone for hypothalamic tumor	N/A
9	2006 [14]	24/F	NA	No	CD68 (+) S-100 (-) CD1a (-)	N/A	N/A
10	2006 [15]	50/F	NA	TAR Syndrome and angiobromas	CD68 (+)	N/A	N/A
11	2008 [4, 16]	13/F	Fingers and palms involvement	No	CD68 (+)	1. Systemic vincristine combined with prednisolone 2. Surgical excision	1. no response 2. difficult to achieve skin closure
12	2009 [2]	34/F	Facial and mucosal involvement	No	CD68 (+) S-100 (+) Factor XIIIa (+) CD1a (-)	Surgical excision	Recurrence
13	2010 [17]	9/M	Facial involvement	No	CD68 (+) MAC387 (+) S-100 (-) CD1a (-)	N/A	N/A
14	2010 [7]	34/F	Laryngeal involvement	No	CD68 (+) S-100 (+) CD1a (-)	N/A	laryngeal Involvement but airway stable
15	2011 [3]	52/F	Facial involvement	No	CD68 (+) CD1a (-)	Surgical excision	No recurrence at 1-year follow-up

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16	2013 [18]	29/M	NA	Anemia	CD68 (+) CD163 (+) S-100 (+) CD1a (-)	Surgical excision	Recurrence
17	2013 [18]	55/M	Ocular involvement	No	CD68 (+) CD1a (-) langerin (-)	systemic steroids	N/A
18	2013 [19]	38/M	Mucosa, palms, and soles were spared	No	CD68 (+) CD163 (+) S-100 (+) CD1a (-)	NA	NA
19	2013 [20]	70/M	Eyelids, mucosa, palms, and soles were spared	Chronic lymphocytic leukemia	CD68 (+) CD163 (+) CD1a (-)	NA	NA
20	2015 [21]	30/M	Facial involvement Ocular involvement	Eale's disease	CD68 (+) S-100 (-)	Imatinib Pazopanib	No response
21	2016 [22]	60/M	Laryngeal involvement	No	CD68 (+) S-100 (-) CD1a (-)	N/A	Died of laryngeal Involvement
22	2017 [23]	12/M	Facial (eyelids) and mucosa involvement		CD68 (+) CD163 (+) S-100 (+) CD1a (-)	NA	NA
23	2017 [24]	78/F	Palms involvement	No	CD68 (+) S-100 (-) CD1a (-)	Methotrexate (15 mg once/week)	Recurrence after discontinuation
24	2019 [25]	11/M	Palms and soles involvement	No	Factor XIIIa (+) CD68 (+) S-100 (-) CD1a (-)	Surgical excision	N/A
25	2019 current case	22/F	Facial (eyelids), mucosa, palms, and soles involvement; Laryngeal involvement	No	CD68 (+) S-100 (+) CD1a (-)	Intermediate-dose cytarabine	Remission

Note: N/A. no available clinical information.

courses of this monotherapy, and efficacy was clearly suggested by the decreased size of the nodules and was confirmed by ¹⁸F-FDG PET/CT.

Conclusions

PNH is a rare type of non-Langerhans cell histiocytosis, diagnosed essentially by its clinical characteristics and typical histopathology. The biological and clinical significance of *XIAP* and *MAPK1* mutations in our patient need to be furtherly discovered. Intermediate-dose cytarabine may be a valuable therapeutic option for PNH, especially for refractory, disseminated PNH. More clinical researches and targeted therapy are warranted in PNH and other histiocytic diseases.

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Disclosure of conflict of interest

None.

Address correspondence to: Xin-Xin Cao, Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. E-mail: caoxinxin@pumch.cn

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Supplementary Table 1. Target gene panel for PNH

ALK	ANKRD50	ANO10	AP3B1	ARAF	ARID1B
ASXL1	ATM	ATP4A	ATP9A	ATRX	B2M
BCL1	BCL2L1	BCOR	BCORL1	BIRC3	BOB
BRAF	BRD4	CALR	CASK	CBL	CCDC168
CCR7	CD274	CDC73	CDH1	CDK6	CDKN1A
CDKN2A	CDKN2B	CEBPA	CEP85	CHEK2	CHMP1A
COL6A6	CSF1R	CSF3R	CTNNB1	DDIT4	DNAH7
DNMT3A	DUSP4	ECE1	EFNA4	EGFR	EMSY
EOMES	ERBB2	ERBB3	ERBB4	ETV6	EZH2
FAS	FBXW7	FCGBP	FGFR2	FGFR3	FLT3
FOXP3	GATA1	GATA2	GNAQ	GNAS	GREB1L
GRK4	HLA-DQA1	HLA-DQB2	HNF1A	HRAS	IDH1
IDH2	ING1	ITIH6	JAK1	JAK2	KDM5A
KDM6A	KDR	KIF5B	KIR2DL4	KIT	KMT2B
KMT2D	KMT2E	KRAS	LYST	MAP2K1	MAP3K1
MAPK1	MAPK8	MAPK14	MDM2	MDM4	MET
MLH1	MSH2	MSH6	MUNC13-4	MYC	MYD88
NCOA2	NCOA4	NCOR2	NEMO	NF1	NFKB1
NOTCH1	NOTCH2	NRAS	NT5DC3	NTRK1	PAX5
PBRM1	PBX1	PCDHA8	PDCD1	PDCD1LG2	PDCD2
PDGFRA	PHIP	PICK1	PIK3CA	PIK3CD	PIK3R2
PKNOX2	PLXNA2	PMS2	PNISR	POLD1	POLE
PRF1	PTEN	PTPN11	RAB27A	RAF1	RB1
RBM10	RET	RICTOR	ROS1	RPS6	RUNX1
RYR2	SCN1A	SEC62	SETBP1	SETD2	SF3B1
SH2D1A	SHOC2	SLC10A6	SLC29A3	SMAD6	SMPD1
SOS1	SPRED1	SREBF1	SRSF2	ST8SIA1	STAG2
STAT3	STK11	STX11	STXBP2	TAP2	TERT
TET2	TLR7	TLR8	TP53	TRBV20OR9-2	TSC1
TTN	U2AF1	UNC13B	UNC13D	VCL	VEGFA
WT1	XIAP	ZRSR2			