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REVIEW

Recurrent Chemotherapy Treated Indeterminate Dendritic Cell Tumor: Case Report and Literature Review

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Abstract: Indeterminate dendritic cell tumor (IDCT) is an extremely uncommon histiocytic and dendritic neoplasms subtype that presents as single or multiple papules. There is currently no standard method for diagnosis and treatment, and the selection of therapeutic approaches is mainly based on successful examples of folk medicine. We describe a case of a pathology diagnosed indeterminate dendritic cell tumor, which shows the presence of CD1a, S100, and CD68, but lack langerin. She was treated with multi-chemotherapy regimens used to treat lymphoma and gained good results short term but was easy to recur. In addition, we reviewed the literature on the effectiveness and safety of chemotherapy in IDCT patients.

Keywords: indeterminate cell histiocytosis, indeterminate dendritic cell tumor, chemotherapy, recurrent, S100 atypical

Introduction

Indeterminate dendritic cell tumor (IDCT), also called indeterminate cell histiocytosis (ICH), was first reported in 1985 by Wood et al.[1] It can be categorized under the "L" group of histiocytosis as per the 2016 Histiocyte Society classification. Pathologically, IDCT exhibits CD1a positivity like Langerhans cell histiocytosis; however, negativity for langerin (CD207) allows for a distinctive differentiation from Langerhans cell histiocytosis.[2] According to both the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours,[3] and the International Consensus Classification of Mature Lymphoid Neoplasms,[4] IDCT belongs to the subgroup of dendritic cell and histiocytic neoplasms.

Its pathophysiology, etiology, and prognostic features are poorly understood due to its rarity. Here we report a multi-chemotherapy treated IDCT patient. Reported IDCT cases using chemotherapy regimens as treatment are reviewed. As far as we know, these kinds of therapies in our patient have never been used in any other Chinese IDCT patient before.

Case Presentation

A 47-year-old female patient in otherwise good health came to the hospital with a 2-month history of diffuse papules with slight pruritus. The papules started on the left forearm without pain, ululation, and purulent discharge and then gradually spread to the trunk, extremities, face, and scalp (Figure 1). Before referral, the patient was diagnosed as blastic plasmacytoid dendritic cell neoplasm (BPDCN), the patient came to our hospital to seek a second opinion.

Pathological consultation in our hospital showed that: S100 (partially +), CD1a (+), Langerin (-), CD4 (+), CD56 (partially +), CD68 (+), CD163 (-), Cyclin D1 (+), Ki67 (LI: 20%), CD3 (-), CD20 (-), CD200 (-), TdT (-), BRAF (-), TCF4 (-), ALK (-), SOX10 (-), according to the clinical manifestations, histopathology, and immunohistochemistry, the diagnosis of indeterminate dendritic cell tumor (IDCT) was made.

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To exclude other malignant tumors, the patient underwent PET-CT (Figure 1), and the possibility of malignant tumor lesions was considered. Bone marrow aspiration and biopsy parallel with karyotype analysis (46, XX[5]), immunophenotyping, and TCR gene testing showed no results of Hematopoietic malignancies. The patient was treated with a course of CHOP plus lenalidomide every three weeks for four courses. The patient's rash improved significantly after the first course of treatment. After completing four courses, the lesions subsided significantly, leaving only pigmentation on the back.

In the next six months, the patient continued to be in remission. Until May 2022, when the rash recurred, the skin biopsy of the back lesion was performed again, and the immunochemistry revealed no significant changes except for S100 compared with the previous one (Figure 1). At the same time, bone marrow aspiration was performed again to exclude malignancy. No notable findings were found. We continued the prior chemotherapy regimen, except for thalidomide instead of lenalidomide, which the patient continued to respond to, but the rash subsided more slowly than before, and she is prone to relapse once drug cessations. The patient did not undergo genetic testing due to economic constraints. She is now treated by the local hospital with another chemotherapy, Oxaliplatin, Gemcitabine, and Betamethasone. According to the latest follow-up phone call, the rash was fading; however, she experienced severe bone marrow suppression midway through the process. Figure 2 shows the timeline of our case.

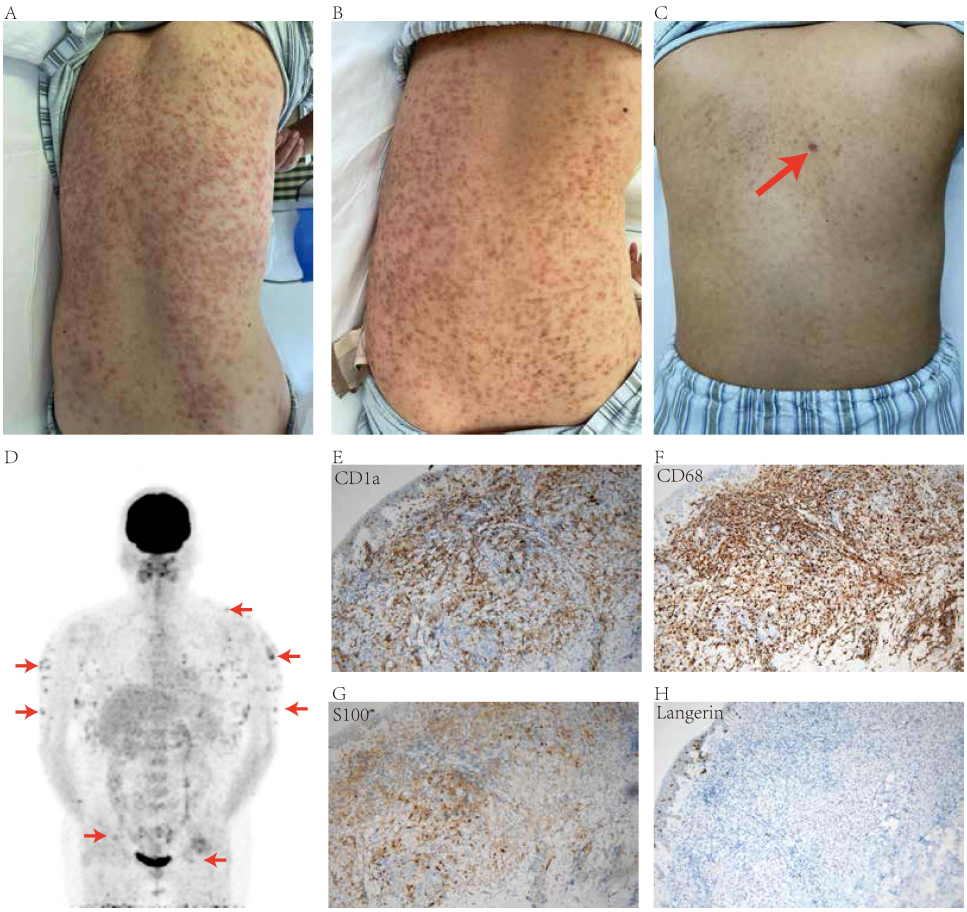

Figure 1 (**A**–**C**) Skin condition before and after treatment. Upon admission, multiple yellowish-red or reddish-brown papules and nodules almost spread throughout the body, with clear boundaries and partial fusion. The back area was the most severe (**A**). After the completion of 4 courses of CHOP+ lenalidomide, the rash subsided significantly, with significant pigmentation on the back (**B**). Two courses of chemotherapy were completed after recurrence, and the rash almost completely subsided with only a small amount of pigmentation on the back (red arrow, biopsy scar after recurrence) (**C**). (**D**) [18F] FDG-PET/CT showed considerable metabolic increases in the skin (the red arrows point to some areas exhibiting heightened metabolic activity). Areas including the upper limbs (upper arm), lower neck, body (back), and the skin/subcutaneous area of the upper thighs of both sides within the detection range, and some of them were accompanied by small nodular shadows. The possibility of malignant tumor lesions was considered. Immunohistochemical studies demonstrated that the histiocytes were positive for CD1a (**E**), CD68 (**F**) and S-100 (**G**) and negative for Langerin (**H**).

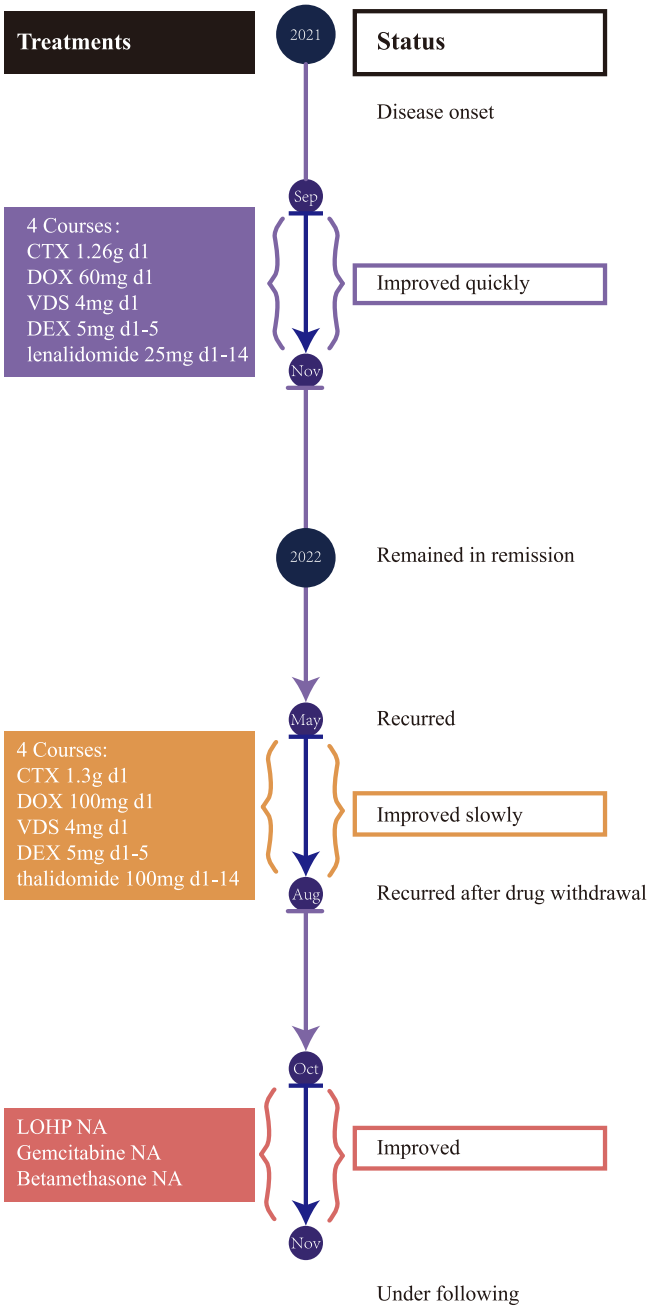

Figure 2 The timeline of this case report.
Abbreviations: CTX, Cyclophosphamide; DOX, doxorubicin; VDS, Vindesine; DEX, dexamethasone; LOHP, Oxaliplatin; GEM, Gemcitabine; NA, not available.

Literature Review

IDCT belongs to a subgroup of dendritic cell and histiocytic neoplasms,[3,4] presenting histological, ultrastructural, and immunophenotypic characteristics of Langerhans cells but missing Birbeck granules. The pathogenesis and etiology of this condition remain unclear.

Epidemiology

Up to now, only roughly 100 cases have been documented in the literature. In China, just approximately ten instances have been reported. IDCT is most frequent in adults and has no gender preference, but it has also been recorded in children.[6]

Pathogenesis

Because of the rarity of IDCT, its pathogenesis is not clear. It has been observed that an itchy rash appears after being bitten by a mosquito or a scabies mite and is subsequently identified as IDCT. Because of this, it is speculated that the reactive inflammatory process is the mechanism of IDCT. Genetic factors are also reported to be involved in the pathogenesis of IDCT but remain obscure. Brown et al[7] detected ETV3-NCOA2 gene mutation in all three of their IDCT patients, while Davick et al[8] found otherwise in their two. Thurner et al[9] successfully kept an IDCT patient with a BRAF V600E mutation in metabolic remission for 23 months using BRAF/MEK Inhibition. New concepts for clinical diagnosis and therapy have emerged due to the identification of these genes. Due to budgetary issues, our patients cannot obtain gene-related testing.

Clinical Presentations

Regarding clinical presentations, most patients exhibit single or numerous papules or nodules confined to the skin. A tiny percentage of individuals experience progression and fusion of lesions, and some of these patients may exhibit unique lesions like leonine facies or pityriasis Rosacea. It has been reported that IDCT can affect extra-skin areas such as the conjunctiva, spine, spleen, and pancreas and that the disease is associated with malignant tumors, particularly hematological tumors[10,11] (myeloid leukemia, follicular lymphoma, etc.), suggesting that we need to run through the examinations of blood and other systems. In our case, papules spread quickly within two months, affecting practically the entire body, but without Extracutaneous involvement.

Diagnosis

The diagnosis of IDCT relies mainly on pathological examination. Our patient was firstly diagnosed with possible BPDCN in her local hospital. Like IDCT, BPDCN are often characterized with cutaneous lesions and can involve bone marrow, lymphonodus and internal organs in different degree, but BPDCN has a more aggressive clinical course and worse prognosis. The pathological consultation in our hospital do show the presence of CD4 and CD56. However, the presence of four or more markers including CD4, CD56, CD123, TCL1, TCF4, and CD303 is imperative for the accurate diagnosis of BPDCN, which our patient did not exhibit, can exclude the diagnosis of BPDCN. Another important differential diagnosis is Langerhans cell histiocytosis (LCH). IDCT could be distinguished from LCH by the absence of langerin expression and Birbeck granules.

Treatment

Various treatments, either alone or in combination, have yielded promising results in IDCT patients, including total skin electron beam therapy, narrow-band UVB therapy, plus ultraviolet A therapy, Topical 5-fluorouracil, topical corticosteroids, pravastatin, bath-psoralen, chemotherapies, thalidomide, and BRAF/MEK Inhibition (if BRAF V600E mutation exists),[8] etc. Given the patient's PET-CT results indicating increased metabolic activity in bilateral inguinal and axillary lymph nodes, coupled with literature suggesting a potential co-occurrence of lymphoma in IDCT cases, we opted for the CHOP regimen. The selection of lenalidomide was based on successful experiences with thalidomide-class drugs in the therapeutic management of IDCT, as identified through literature retrieval. During treatment, our patient developed bone marrow suppression and decreased blood cells, so the 3rd course of lenalidomide was only taken for seven days. The patient responded sensitively to this chemotherapy regimen, and the lesions improved significantly at the end of the first course, with only dorsal hyperpigmentation remaining after completing four courses. She maintained remission for about six months but relapsed.

We reviewed the current examples of IDCT with cutaneous symptoms treated with chemotherapy medications to assess the efficacy and safety of chemotherapy drugs[1,5,11–30] (Table 1). We found that remission and relapse occurred in 8 out of 26 chemotherapy-treated patients reported to date.[5,11,16,24,25] Among the reported cases, six of them achieved complete remission. The average follow-up period was 47 months (range: 10–114 months). Interestingly, half of the patients experienced a process of remission and subsequent relapse.[20,22] Additionally, 6 out of 26 reported cases died, all

Table 1 Reported Cases of IDCT with Cutaneous Symptoms Treated with Chemotherapy Medications

Author (Year)	Gender	Age	Presentation: MF/SF	NGS	Mutation Detected	Extracutaneous Involvement	Treatment	Outcome	FU(Mo)	Reference
Wood (1985)	Female	25	MF	No		No	1. Steroid injections; 2. vinblastine sulfate	Did well with treatment once a month (4 y); flare-up without treatment; 33 mo without recurrence. RR then CR	114	[1]
Kolde (1985)	Male	36	MF	No		MastCL	Vincristine, daunorubicin hydrochloride (Daunoblastina), and asparaginase	DOD	72	[26]
Segal (1991)	Male	29	MF	No		FL, AML	1. Lomustin; 2. carmustine; 3. CTX, vincristine, and prednisone; 4. CTX, doxorubicin, VP-lb /cytarabine, vin- cristine, methotrexate with leucovorin, bleomycin, and pred- nisone	DOD	45	[27]
Flores-Stadler (1999)	M	0	MF	No		Bone marrow	CTX, doxo-rubicin, vincristine, and prednisone	DOD	20	[28]
Rodriguez-Jurado (2003)	F	13	MF	No		No	Pure coal tar and 5% 5-FU cream	PR		[29]
Caputo (2005)/ case 1	Male	32	MF	No		No	1. CTX; 2. etoposide; 3. Vinylsulfatase and Methylprednisolone; 4.2-Chlorodeoxyadenosine	Experienced remission and relapse processes during treatment and finally induced a complete remission after 4-year treatment. RR then CR	48	[25]
Caputo (2005)/ case 2	Male	36	MF	No		No	1. CTX; 2. etoposide; 3. acelastine and methylprednisolone	Experienced remission and relapse processes during treatment, currently without therapy and free of lesions. RR then CR	60	[25]

(*Continued*)

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Table 1 (Continued).

Author (Year)	Gender	Age	Presentation: MF/SF	NGS	Mutation Detected	Extracutaneous Involvement	Treatment	Outcome	FU(Mo)	Reference
Vener (2007)	Male	39	MF	No		AML	1. Oral CTX; 2. etoposide(iv); 3. vinblastin and ethylprednisolone	Repeated remission and recurrence; the fourth year was diagnosed of AML and died of acute respiratory failure that year. RR then DOD	48	[11]
Yin (2009)	Female	30	MF	No		No	Thalidomide and isotretinoin	The lesion disappeared within 1 year; follow-up after 3 years without recurrence. CR	48	[22]
Cheuk (2009)	Female	44	MF	No		No	1. CTX, epirubicin, vincristine and prednisone; 2. VM-26 and vinblastine; 3. herbal medicine; 4. etoposide	Responded quite dramatically to chemotherapy, and relapse often occurred on cessation of therapy: SD with RR	120	[24]
Ventura (2010)	Male	62	MF	No		No	Thalidomide	2 months: gradual regression; 7 months: almost complete remission; 1 month after remission: diagnosed of an acute monocytic leukemia and died 1 month later due to a respiratory failure. DOD	10	[23]
Tóth (2011)	Male	15	MF	No		No	1. 5-FU, repeatedly cryotherapy and cauterization: ineffective; 2. transfer to thalidomide	8 months: healed with pigmentation; 3 years: without recurrence. PR	44	[20]
Ozono (2011)	M	1	MF	No		JMML	1. vincristine, Ara-C, and prednisolone; 2. 6MP; 3. HSCT	PR	9	[30]
Fournier (2011)	Female	65	MF	No		No	MTX	Complete clinical remission after 2 months of treatment, relapse during dose reduction:SD with RR	5	[5]

Bettington (2011)	Male	40	MF	No		FL, lymph nodes	Multiple regimens to treat FL: CVP, CVP-R and CHOP	4 months after diagnosed with IDCT, he died due to the development of end-stage liver disease, which limited the treatment.:DOC	4	[21]
Chen (2018)	Male	31	MF	N0		No	MTX, no response, transfer to isotretinoin and thalidomide	Improvement on skin, under follow up: SD	48	[17]
Zhou (2019)	Male	37	MF	Yes	No	No	Corticosteroids, vinca alkaloids, CTX	Utilizing a range of treatments, yet constantly experiencing remission and relapse within 5 years. SD with RR	60	[16]
Fischer (2021)	Female	55	MF	No		No	Thalidomide	6 months: lesion progress:PD	6	[15]
Xu (2017)	M		MF	No		No	Thalidomide	PR	10	[18]
Xu (2017)	F	53	MF	No		No	Methotrexate	CR	10	[18]
Xu (2017)	M		MF	No		No	Methotrexate	CR	10	[18]
Xu (2017)	F		MF	No		No	Thalidomide	PR	10	[18]
Lie (2022)	Male	70	MF	No		No	Initial treatment with psoralen and PUVA for 4 months: ineffective transfer to MTX	6 months: significant improvement:PR	10	[13]
Belina (2022)	Female	62	MF	Yes	ETV3-NCOA2	No	MTX and NBUVB	Sustained improvement in cutaneous lesions:PR		[14]
Xia (2022)	Female	26	MF	Yes	No	No	Thalidomide followed by prednisolone	Resistant to treatment:SD	36	[12]
Li (2022)	Female	47	MF	No		No	CHOP plus lenalidomide/ thalidomide; Oxaliplatin, Gemcitabine and Betamethasone	Remission and recurrence during CHOP, lesion is regressing with another chemotherapy. SD with RR	12	

Abbreviations: MF, multi focal; SF, single focal; FU, follow up months; CMML, chronic myelomonocytic leukemia; FL, follicular lymphoma; CTX, cyclophosphamide; 5-FU, 5-fluorouracil; MTX, methotrexate; CVP/CVP-R, cyclophosphamide, vincristine and prednisone plus or minus rituximab; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone; PUVA, Psoralen and ultraviolet light A; NBUVB, Narrowband ultraviolet B; 6MP, 6-mercaptopurine; HSCT, stem cell transplantation; CR, complete remission; PR, partial remission; RR, remission and relapse; DOD, dead of disease; DOC, dead of other cause; PD, progressive disease.

of them are found to have haematological neoplasia after chemotherapy initiated.[11,23] Although it has been reported that IDCT is related to malignant tumors, the carcinogenic effect of chemotherapy drugs themselves cannot be ruled out.

Conclusion

In conclusion, we report a case of IDCT presenting with multiple papules, markedly improving after treatment but recently recurred. At the same time, the expression of S100 changed from partially positive to positive. I believe our case has contributed to understanding IDCT and the complex adjustment mechanism of S100 expression. Additionally, after analyzing chemotherapy treated IDCT patients, we suggest a more cautious chemotherapy medication selection. Long-term follow-up is required due to the link between lymphoproliferative illness and hematological malignancies.

Ethics Statement

The patients in this manuscript have given written informed consent to publication of their case details and any accompanying images. No institutional approval is required for the publication of this case.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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