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Original Article

Outcomes of cutaneous indeterminate dendritic cell tumors: case report and pooled analysis

Lihong Bai[1*], Jihui Kang[2*], Jiayan Lian[3], Wenlin Xie[3], Chuangjie Cao[2], Zhongwei Lin[4], Chengyun Dou[5], Zhuo Wang[2]

[1]The Division of Pulmonary and Critical Care Medicine, [2]Depatrtment of Pathology, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [3]Department of Pathology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China; [4]Department of Cardiology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China; [5]Department of Infectious Disease, The First Affiliated Hospital of University of South China, Hengyang, China. [*]Equal contributors.

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Abstract: The goal of this study was to investigate the prognostic impact of indeterminate dendritic cell tumors (IDCTS). Cases of cutaneous IDCT both in the literature and our reported case were collected and analyzed. With our patient, 65 cases of cutaneous IDCTs were evaluated. Median age of included cases was 48-year old. Patients with hematological neoplasia were 17-year older than non-hematological neoplasia group. Patients older than 60-year had significant lower overall survival (OS) rate than patients younger than 60-year (P=0.016). OS rate of hematological neoplasia patients was significantly lower than non-hematological neoplasia patients. In addition, histological feature of prominent nucleoli had significant higher OS rate than no obvious nucleoli group. IDCT patients with hematological neoplasia were typically of older age, and this group of patients had a worse prognosis. Histological feature of prominent nucleoli also has a worse prognosis.

Keywords: Dendritic cells, histiocytosis, prognosis, pathology, neoplasms

Introduction

Indeterminate dendritic cell tumors (IDCTs) are an extremely rare disease characterized by a proliferation of cells that express CD1a and S-100 protein. In contrast to tumors derived from langerhans cells, IDCs don't have Birbeck granules. Immunohistochemistry was first defined in 1985 as cells characterized for CD1a and S-100 positive but lacking Birbeck granules [1]. Since then, several case reports have supported the concept of IDCTs (also known as indeterminate cell histiocytosis, is a neoplastic proliferation of spindled to ovoid cells with phenotypic features similar to those of normal indeterminate cells, the alleged precursor cells of Lanerhans cells.), as IDCTs are usually restricted to the skin. In 2016, IDCT was classified into "L" (Langerhans) group in a revised WHO edition [2].

Despite increasing knowledge of cutaneous IDCTs, they are easily misdiagnosed and often not considered due to its rarity. Therefore, in this study, we have analyzed the histological features and outcomes of our case. Additionally, a literature review summarizing the main features of cutaneous IDCTs is presented.

Materials and methods

Tissue specimens and pathological analysis

A patient was identified cutaneous IDCT at the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, People's Republic of China. The patient's clinical features, MRI, and pathological features were recorded.

The resected sample of our reported case was fixed in 10% buffered formalin and embedded in paraffin. They were sectioned in 4-μm slices and stained with hematoxylin and eosin. Immunohistochemical study was performed using the following primary antibodies: pan-cytokeratin, EMA, CD1a, S100, CD68, langerin, Myo-

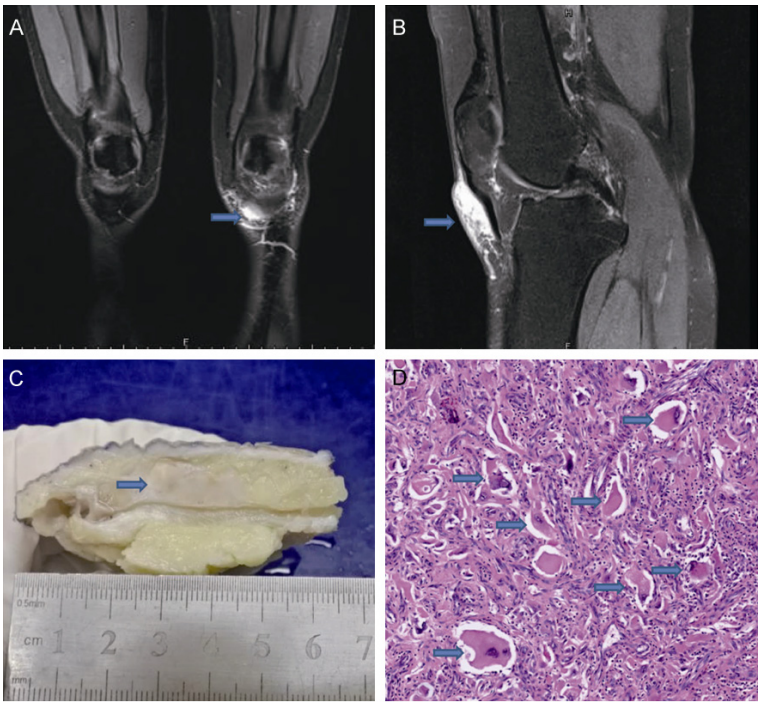

Figure 1. MRI demonstrated the tumor on left keen (A and B). The section was solid, white-grayish, fine and smooth, no bleeding and necrosis (C). Hematoxylin and eosin (HE) demonstrated the histological features of the tumor with abundant, eosinophilic cytoplasm and large, round, partially cleaved nuclei (arrows pointing representative cells, D).

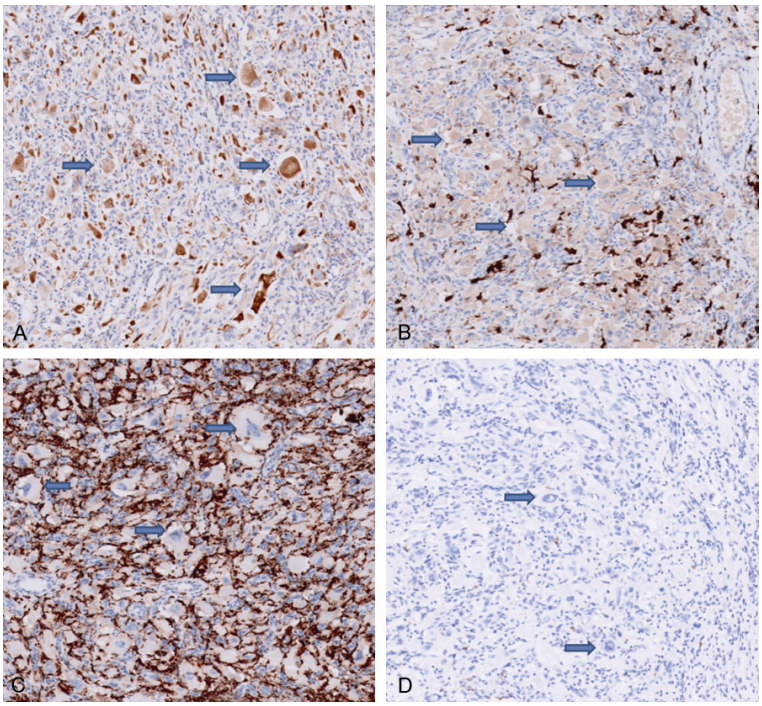

Figure 2. Immunohistochemical staining shows tumor cell are positive for CD1a (A), weak positive for S-100 (B), negative for CD68 (C) and Langerin (D).

genin, MyoD1, Bcl2, CD34, Desmin, Actin, HMB45, MelanA, CD21, CD35, CD61, MPO, CD23, Syn, all from Dako (Glostrup, Denmark). Immunoreactivity was detected using the Dako labeled streptavidin-biotin detection kit according to the manufacturer's recommended procedures.

Analysis of cases of cutaneous IDCT in the literature

This study chose the databases of PubMed and was assessed through NCBI. The search term was "indeterminate dendritic cell". The publication dates ranged from Jan.1, 1984 to Oct.1, 2017. Included article types had definite diagnosis of IDCT and had cutaneous lesion starting time to last follow-up survival (overall survival, OS). Of these, 62 articles were obtained in Pubmed and 22 were excluded (Tables S1 and S2). The remaining literature was assessed and 65 cutaneous cases of IDCT including our report were studied.

Pooled analysis

Cases of cutaneous IDCTs both in the literature and our reported case were collected and analyzed. The endpoint outcome were patient's death and alive. The extracted data were age, gender, cutaneous lesion pattern, history or concurrent disease, overall survival (survival from skin lesions) and outcome.

Statistical analysis

The difference of age between cutaneous lesion pattern, history or concurrent disease was estimated by Kruskal-Wallis test. Kaplan-Meier survival curves were estimated for overall

Table 1. General characteristics of included cases

Clinical features	Number
Age <60:Age ≥60	43 (66.2):22 (33.8)
Male:Female	36 (55.4):29 (44.6)
Hematological neoplasia:non-hematological neoplasia (n=65)	12 (18.5):53 (81.5)
Non-hematological neoplasia	53 (81.5)
Otherwise healthy	46 (70.8)
Having other disease*	7 (10.8)
Single lesion:Multiple lesions (n=65)	30 (46.2):35 (53.8)
Documented Alive:Dead (n=65)	56 (86.2):9 (13.8)

*including breast cancer, conjunctiva lesions, bone lesions, diabetes, Skin cancer, HBV, Colon cancer and so on.

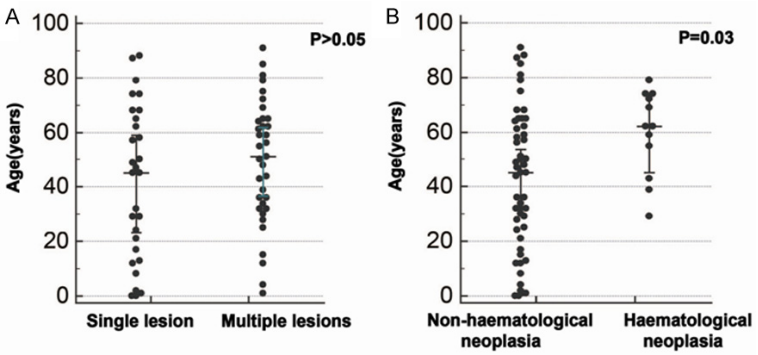

Figure 3. Median age has not any significant differences between cutaneous lesion patterns (A). Median age of patients with hematological neoplasia was 17 years older than non-hematological neoplasia patients (B).

survival (OS) rate. Log-rank test was used to indicate the difference of survival curves. All tests were two-sides and significant level was 0.05. All analyses were conducted by SPSS 20.0 (IBM, Inc.).

Results

The presentation of our IDCT case

An otherwise healthy 32-year-old female with a 1.2-year history of an asymptomatic nodule on her left knee was referred for 3 months pain on her knee after working. Pain was relieved gradually after resting. Physical examination revealed a nodule on her left knee. The epidermis on the nodule was intact and no significant findings elsewhere. MRI revealed that the mass was in dermis and involved the patellar ligament (**Figure 1A**, **1B**).

An excision sample from the nodule showed large histiocyte-like cells and spindle cells in the middle dermis (**Figure 1C**). Histiocyte-like cells had abundant and eosinphilic cytoplasm with large, round and partially cleaved nuclei (**Figure 1D**). Spindle cells were around the large cells, and also had eosinphilic cytoplasm and spindle nuclei. Immunohistochemical analysis demonstrated that the large histiocyte-like cells were positive for CD1a (**Figure 2A**), weak positive for S100 (**Figure 2B**) and negative for CD68 (**Figure 2C**), langerin (**Figure 2D**), Myogenin, MyoD1, Bcl2, CD34, Desmin, pan-CK, EMA, Actin, HMB45, MelanA, CD21, CD35, CD61, MPO, CD23, Syn. Spindle cells were positive for CD68, partially positive for CD1a, partially weak positive for S100, and negative for langerin, Myogene, MyoD1, Bcl2, CD34, Desmin, pan-CK, EMA, Actin, HMB45, MelanA, CD21, CD35, CD61, MPO, CD23, Syn. Based on these clinicopathological and immunohistochemical results, the diagnosis was confirmed as IDCT. After a follow-up for 6 months, the lesions resolved without reoccurring.

Pooled analysis

With our patient, we evaluated 65 cases of cutaneous IDCTs. Median age of included cases was 48-year old with 33.8% patients older than 60-year old. 55.4% were male. 18.5% had hematological neoplasia and 10.8% had other disease. 53.8% were multiple lesions and 13.8% were documented death (**Table 1**). Median age was similar between histopathological factor of cutaneous lesion patterns (single lesion or multiple lesions) (**Figure 3A**). However, median age was 62-year old among patients with hematological neoplasia, 17 years older than non-hematological neoplasia patients (**Figure 3B**, P=0.03).

Patients older than 60-year had significant lower OS rate than patients younger than 60-year

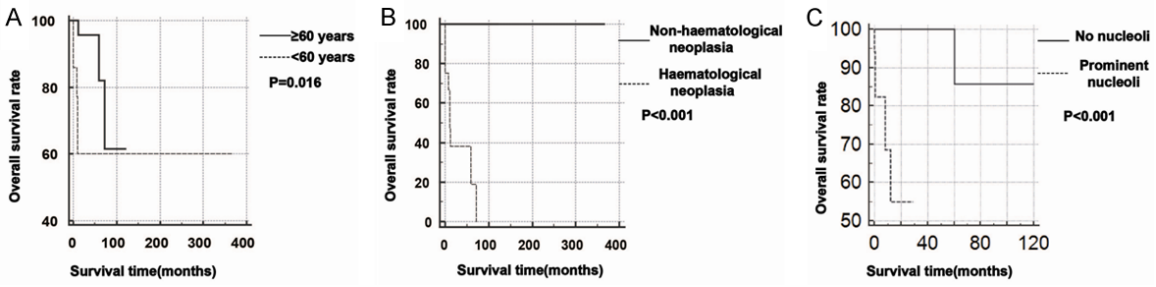

Figure 4. Patients with an older age had lower OS rate significantly (A). Patients with hematological neoplasia had lower OS rate than non-hematological neoplasia patients (B). Patients with prominent nucleoli had lower OS rate than no nucleoli patients (C).

Table 2. Overall survival rate between different histological features of cutaneous IDCTs

Histological features	Available Cases (N)	Groups (N:N)	Overall survival rate (%)	*P* value
*Cell size	49	Large:Small = 40:9	87.5:77.8	>0.05
Cytoplasm	48	Abundant:Minor = 41:7	85.7:85.3	>0.05
Nucleoli	46	Prominent:None = 17:29	70.6:96.6	<0.001
Atypia	47	Distinctive:Little = 22:25	81.8:88.2	>0.05
Multinucleated giant cell	46	Exist:None = 12:34	91.7:85.3	>0.05
Lymphocytes	45	Abundant:Few = 34:11	91.2:90.8	>0.05

*Cell size: large cell means tumor cell larger than 3 times red cells; small cell means tumor cell smaller than 3 times red cells.

(72.7%:93%, P=0.016, **Figure 4A**). Gender and cutaneous lesion pattern were not associated with OS. OS rate of hematological neoplasia patients was lower than non-hematological neoplasia patients with a significance of P< 0.001 (25%:100%, **Figure 4B**).

The shape of the tumor cells of IDCTs was variable. The spindled, ovoid, large, round or pleomorphic cells were presented. Cytoplasm was typically eosinophilic and abundant. Lymphocytes and multinucleated giant cells were often present. Most cases were mainly large cells with abundant cytoplasm (**Table 2**). Other histological features were summarized in **Table 2**. Histological features of cell size, cytoplasm, atypia, multinucleated giant cell and lymphocytes were not associated with OS, except prominent nucleoli with 70.6% OS rate lower than none nucleoli group (P<0.001, **Figure 4C**).

Discussion

IDCT is a rare neoplasm, and most IDCTs often cause as diagnostic challenge for pathologists who are not familiar with this entity. Apart from other known histiocytosis, the diagnostic criteria of IDCT have some distinct immunophenotypic features [3]: CD1a+, S-100+/-, Langerin- [4, 5] or lacking Birbeck granules. It was classified into "L" group in a revised WHO edition in 2016 [2]. In our case, we first considered mesenchymal tumor including rhabdomyosarcoma, undifferentiated high grade plemorphic sarcoma or fibrosarcoma for more than 10 immunohistochemical markers, and none of them was positive. Therefore, second group of immunohistochemical markers including "the langerhan cells group" was conducted and confirmed the IDCT diagnosis. ETV3-NCOA2 translocation is a novel factor in diagnosing IDCT [6] according literature reports, and need further investigation in making consensus.

IDCT is always restricted to the skin without systemic symptoms [3, 7]. IDCT cases were reviewed with cutaneous lesions for this analysis. Most IDCTs occur in adults without predilection for either sex [5, 8] which is consistent with our results. The most concerning outcome regarding the prognosis of IDCT was the patients with hematologic disorders or evolution to hematologic disorders, with death having occurred in some instances [5, 9-12] even after treatment with chemotherapeutics. Therefore, we propose a pooled analysis for IDCT for the histopathological prognosticators. In fact, IDCT was classified into "L" group which is considered a myeloid neoplasm arising from constitutive activation of MAPK pathway, generally due to BRAF mutations, during myeloid differentiation [2, 13]. However, the discovery of ETV3-

NCOA2 translocations in 3 cases of IDCT suggests that it might represent a distinct clonal neoplasm [6]. We found that patients with hematological neoplasia were 17-year older than non-hematological neoplasia group. Patients older than 60-years of age had significant lower OS rate than patients younger than 60-year. Such phenomenon was consistent with the natural rule. OS rate of hematological neoplasia patients was significantly lower than non-hematological neoplasia patients. This result indicated that patients with hematological neoplasia had a worse prognosis.

In Horna P et al. review [3], they summarized the places of IDCTs and cutaneous lesions with the most frequency of 91%. However, in few studies that were reviewed did they contain histopathological features of IDTCs. In assessing available descriptions and pictures, the histological features of IDTCs were summarized. Prominent nucleoli was observed to have a lower OS rate. This result was in accordance with the prognosis of major malignant tumors.

In conclusion, IDCTs patients with hematological neoplasia were likely older age (median 62-year old), and this group of patients had a worse prognosis. In addition, prominent nucleoli indicated a worse prognosis.

Acknowledgements

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Disclosure of conflict of interest

None.

Address correspondence to: Zhuo Wang, Department of Pathology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China. Tel: +86 20 28823350; E-mail: wangzh25@mail.sysu.edu.cn

References

[1] Wood GS, Hu CH, Beckstead JH, Turner RR and Winkelmann RK. The indeterminate cell proliferative disorder: report of a case manifesting as an unusual cutaneous histiocytosis. J Dermatol Surg Oncol 1985; 11: 1111-1119.

[2] Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, Requena-Caballero L, Jordan MB, Abdel-Wahab O, Allen CE, Charlotte F, Diamond EL, Egeler RM, Fischer A, Herrera JG, Henter JI, Janku F, Merad M, Picarsic J, Rodriguez-Galindo C, Rollins BJ, Tazi A, Vassallo R, Weiss LM and Histiocyte S. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016; 127: 2672-2681.

[3] Horna P, Shao H, Idrees A, Glass LF and Torres-Cabala CA. Indeterminate dendritic cell neoplasm of the skin: a 2-case report and review of the literature. J Cutan Pathol 2017; 44: 958-963.

[4] Ratzinger G, Burgdorf WH, Metze D, Zelger BG and Zelger B. Indeterminate cell histiocytosis: fact or fiction? J Cutan Pathol 2005; 32: 552-560.

[5] Rezk SA, Spagnolo DV, Brynes RK and Weiss LM. Indeterminate cell tumor: a rare dendritic neoplasm. Am J Surg Pathol 2008; 32: 1868-1876.

[6] Brown RA, Kwong BY, McCalmont TH, Ragsdale B, Ma L, Cheung C, Rieger KE, Arber DA and Kim J. ETV3-NCOA2 in indeterminate cell histiocytosis: clonal translocation supports sui generis. Blood 2015; 126: 2344-2345.

[7] Ghanadan A, Kamyab K, Ramezani M, Goodarzi A, Daneshpazhooh M, Balighi K, Ansari M, Mirfallah Nassiri SF and Daklan S. Indeterminate cell histiocytosis: report of a case. Acta Med Iran 2014; 52: 788-790.

[8] Wang CH and Chen GS. Indeterminate cell histiocytosis: a case report. Kaohsiung J Med Sci 2004; 20: 24-30.

[9] Vitte F, Fabiani B, Benet C, Dalac S, Balme B, Delattre C, Vergier B, Beylot-Barry M, Vignon-Pennamen D, Ortonne N, Algros MP, Carlotti A, Samaleire D, Frouin E, Levy A, Laroche L, Theate I, Monnien F, Mugneret F and Petrella T. Specific skin lesions in chronic myelomonocytic leukemia: a spectrum of myelomonocytic and dendritic cell proliferations: a study of 42 cases. Am J Surg Pathol 2012; 36: 1302-1316.

[10] Bettington A, Lai JK and Kennedy C. Indeterminate dendritic cell tumour presenting in a patient with follicular lymphoma. Pathology 2011; 43: 372-375.

[11] Ventura F, Pereira T, da Luz Duarte M, Marques H, Pardal F and Brito C. Indeterminate cell histiocytosis in association with acute myeloid leukemia. Dermatol Res Pract 2010; 2010: 569345.

[12] Vener C, Soligo D, Berti E, Gianelli U, Servida F, Ceretti E, Caputo R, Passoni E and Lambertenghi Deliliers G. Indeterminate cell histiocytosis in association with later occurrence of acute myeloblastic leukaemia. Br J Dermatol 2007; 156: 1357-1361.

[13] El Demellawy D, Young JL, de Nanassy J, Chernetsova E and Nasr A. Langerhans cell histiocytosis: a comprehensive review. Pathology 2015; 47: 294-301.

Table S1. Case reports of indeterminate dendritic cell neoplasmincluded in the discussed literature review

Clinical presentation	Reference
Skin, single lesion	1. Amo Y, et al. *J Dermatol*. 2003; 30: 751-754.
	2. Bakry OA, et al. *Rare Tumors*. 2013; 5: e13.
	3. Brown RA, et al. *Blood*. 2015; 126: 2344-2345.
	4. Deng A, et al. *J Cutan Pathol*. 2008; 35: 849-854.
	5. Ferran M, et al. *Pediatr Dermatol*. 2007; 24: 253-256.
	6. Jang KA, et al. *Pediatr Dermatol*. 2000; 17: 364-368.
	7. Levisohn D, et al. *Arch Dermatol*. 1993; 129: 81-85.
	8. Miracco C, et al. *Am J Dermatopathol*. 1988; 10: 47-53.
	9. Ratzinger G, et al. *J Cutan Pathol*. 2005; 32: 552-560.
	10. Rezk SA, et al. *Am J Surg Pathol*. 2008; 32: 1868-1876.
	11. Roh J, et al. *J Pathol Transl Med.*2016; 50: 78-81.
	12. Vitte F, et al. *Am J Surg Pathol*. 2012; 36: 1302-1316.
Skin, multiple lesions	13. Bard S, et al. *Pediatr Dermatol*. 2011; 28: 524-527.
	14. Bettington A, et al. *Pathology*. 2011; 43: 372-375.
	15. Burns MV, et al. *J Am Acad Dermatol*. 2011; 64: e85-86.
	16. Caputo R, et al. *Br J Dermatol*. 2005; 153: 206-207.
	17. Caputo R, et al. *J Am Acad Dermatol*. 2007; 57: 1031-1045.
	18. Cheuk W, et al. *Am J Surg Pathol*. 2009; 33: 1261-1263.
	19. Contreras F, et al. *Am J Dermatopathol*. 1990; 12: 396-401.
	20. Fournier J, et al. *J Dermatol*. 2011; 38: 937-939.
	21. Ghanadan A, et al. *Acta Med Iran*. 2014; 52: 788-790.
	22. Haimovic A, et al. *Dermatol Online J*. 2014; 20.
	23. Ishibashi M, et al. *Clin Exp Dermatol*. 2008; 33: 301-304.
	24. Logemann N, et al. *Dermatol Online J*. 2013; 19: 20031.
	25. Malhomme de la Roche H, et al. *Br J Dermatol*. 2008; 158: 838-840.
	26. Mo X, et al. *Medicine.* 2015; 94: e1443.
	27. Oh CW, et al. *J Cutan Pathol*. 2016; 43: 158-163.
	28. Ratzinger G, et al. *J Cutan Pathol*. 2005; 32: 552-560.
	29. Rodriguez-Jurado R, et al. *Arch Pathol Lab Med*. 2003; 127: 748-751.
	30. Rosenberg AS, et al. *J Cutan Pathol*. 2001; 28: 531-537.
	31. Segal GH, et al. *Cancer*. 1992; 70: 547-553.
	32. Sidoroff A, et al. *Br J Dermatol*. 1996; 134: 525-532.
	33. Strahan JE, et al. *Arch Dermatol*. 2010; 146: 346-347.
	34. Toth B, et al. *Pathol Oncol Res*. 2012; 18: 535-538.
	35. Vener C, et al. *Br J Dermatol*. 2007; 156: 1357-1361.
	36. Ventura F, et al. *Dermatol Res Pract*. 2010; 2010: 569345.
	37. Vitte F, et al. *Am J Surg Pathol*. 2012; 36: 1302-1316.
	38. Wang CH, et al. *Kaohsiung J Med Sci*. 2004; 20: 24-30.
	39. Wood GS, et al. *J Dermatol Surg Oncol*. 1985; 11: 1111-1119.
	40. Yin R, et al. *JAm Acad Dermatol*. 2010; 63: e3-5.

Table S2. Case reports excluded from our literature review

Reference	Reason for exclusion
1. Buser L, et al. Pathobiology. 2014; 81: 199-205.	Non-cutaneous IDCT
2. O'Malley DP, et al. Ann Diagn Pathol. 2015; 19: 113-116.	
3. Rezk SA, et al. Am J Surg Pathol. 2008; 32: 1868-1876.	
4. Vasef MA, et al. Am J Clin Pathol. 1995; 104: 696-701.	
5. Chen M, et al. Hum Pathol. 2012; 43: 307-311.	
6. Martin Flores-Stadler E, et al. Med Pediatr Oncol. 1999; 32: 250-254.	
7. Johnstone K, et al. Pathology. 2016; 48: 628-631.	A definitive diagnosis of IDCT was not rendered by authors.
8. Berti E, et al. *Arch Dermatol*. 1988; 124: 1250-1253.	
9. Frater JL, et al. *J Cutan Pathol*. 2006; 33: 437-442.	
10. Hui PK, et al. *Am J Dermatopathol*. 1987; 9: 129-137.	
11. Martins MT, et al. *Oral Oncol.* 2004; 40: 341-347.	
12. Pastor-Jane L, et al. *Am J Dermatopathol*. 2011; 33: 516-520.	
13. Tardio JC, et al. *Am J Dermatopathol*. 2013; 35: e57-59.	
14. Ventarola DJ, et al. *Arch Dermatol*. 2011; 147: 995-997.	
15. Daoud MS, et al. Cutis. 1997; 59: 27-31; quiz 32.	Not enough information provided.
16. Fernandez-Flores A, et al. Cesk Patol. 2008; 44: 37-39.	
17. Brown RA, et al. Blood. 2015; 126: 2344-2345.	
18. Calatayud M, et al. Cornea. 2001; 20: 769-771.	
19. Dalia S, et al. *Cancers (Basel)*. 2014; 6: 2275-2295.	
20. Fedoriw Y, et al. Leuk Lymphoma. 2014; 56: 1132-1133.	
21. Grau-Massanes M, et al. *J Cutan Pathol.* 1992; 19: 526-32.	
22. Kolde G, et al. J Am Acad Dermatol. 1986; 15: 591-597.	