Indeterminate Dendritic Cell Tumor

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Published in Atlas Database: December 2018

Online updated version : http://AtlasGeneticsOncology.org/Anomalies/IndeterminDendritCellID1728.html
DOI: 10.4267/2042/70612

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Abstract

Indeterminate dendritic cell tumor (IDCT) is an extremely rare hematopoietic malignancy. The indeterminate cells are considered a precursor stage of skin dendritic or Langerhans cells. IDCT is frequently misdiagnosed as another dendritic or histiocytic cell neoplasm, with Langerhans cell histiocytosis being the most common. Recently, cases with recurrent ETV3/NCOA2 translocation have been described.

Keywords
Indeterminate Dendritic Cell Tumor; ETV3; NCOA2; BRAF

Identity

Other names
Dendritic Cell Tumor, Indeterminate Cell Histiocytosis

Clinics and pathology

Disease

Indeterminate Dendritic Cell Tumor (IDCT) is an extremely rare hematopoietic malignancy (Horna P et al., 2017). The etiology of IDCT remains unknown. An association between IDCT and other hematologic neoplasms has been reported (like B-cell lymphomas, acute myeloid leukemia or chronic myelomonocytic leukemia (CML)) (Rezk SA et al., 2008; Joo JW et al., 2018). Recently cases with recurrent ETV3/NCOA2 translocation have been described, being a potential therapeutic and diagnostic tool and proving that IDCT is a clonal entity (Brown RA et al., 2005). The indeterminate cells (IC) are considered a precursor stage of skin dendritic or Langerhans cells (Joo JW et al., 2018). IDCTs present with the same morphological, ultrastructural and immunophenotypic features than Langerhans cell histiocytosis (LCH) (Rezk SA et al., 2008). Therefore LCH is one of the main disorders that should be excluded. Features that help differentiate LCH from IDCT are the absence of Birbeck granules and the non-expression of langerin (CD 207) in IDCT cells (Ratzinger G et al., 2005). Neoplastic cells also express S100, CD1a, and CD68. IDCT mostly presents with skin involvement with one or more lesions like plaques, nodules or papules; but exceptionally affects lymph nodes or spleen (Dalia S et al., 2014). The clinical course is relatively benign; even so, it could vary from spontaneous regression (Ratzinger G et al., 2005) to stable disease or to progression and to recurrence (Joo JW et al., 2018). There is no standard treatment regimen and several approaches have been carried out. Given the good prognosis, aggressive systemic treatments are not usually performed (Joo JW et al., 2018), and most lesions can be removed with surgery (Davick JJ et al., 2018).

PATHOGENESIS It is not well described and remains unknown. ICs are considered pre-Langerhans cells, which during migration towards epidermis are not able to incorporate Birbeck granules (Tan SK et al., 2017). Association with other neoplasms has been described and in some cases, a clonal relationship between IDCT and those tumors was present (Rezk SA et al., 2008). These findings, in CML cases, could be explained by the capacity of malignant monocytes to differentiate into dendritic cells (Horna P et al., 2017). Despite the existence of clonal origin, morphologic and immunophenotypic characteristics are the same in isolated IDCTs (Horna P et al., 2017). Scabies mite infestations have also been postulated to play a role...
on IDCT etiopathogenesis (Hashimoto K et al., 2000). Demonstration of BRAF V600E mutation (O’Malley DP et al., 2015) and ET3V/NCOA2 gene fusion shed light on biology cell origin of IDCT, but further studies are needed to describe its implication.

**Epidemiology**

IDTC is a very uncommon disease; in fact, between 1985 and 2016 only 85 cases were reported in the literature (Davick JJ et al., 2018). The median age at diagnosis is around 45 years, with a slight predominance in male gender (Davick JJ et al., 2018).

**Clinics**

The vast majority of IDCT cases present cutaneous involvement (88%), whereas locations like lymph nodes (9%) and spleen (2.3%) are less common (Davick JJ et al., 2018). Plaques, nodules or papules are some of those skin lesions which often involucrate head, chest, trunk, back or extremities (Horna P et al., 2017). The tumor usually affects the dermis and, in some cases, the epidermis could also be compromised (Joo JW et al., 2018). Systemic symptoms, communs in others dendritic/histiocytic cell neoplasms, are infrequent in IDCT (Roh J et al., 2016). It is important to highlight the indolent clinical course and the predilection for the skin in the cases of IDCT, in comparison with LCH, the main differential diagnosis disorder.

**Pathology**

IDCT and LCH share morphologic features, being difficult to distinguish between them. Dermal lesion presents a diffuse infiltration of oval mononuclear cells, with irregular nuclear grooves and abundant cytoplasm (Dalia S et al., 2014). The absence of eosinophilic infiltrates and epidermotropism (characteristic of LSC) supports the diagnosis of IDCT (Rezk SA et al., 2008; Horna P et al., 2017). Electron microscopy will strengthen our IDCT diagnosis showing the lack of Birbeck granules in the neoplastic cells (Rezk SA et al., 2008).

**IMMUNEPHENOTYPE** Represents an essential diagnostic tool, that combined with electron microscopy, allow us to differentiate IDCT from LCH. Neoplastic cells characteristically express CD1a, S100, and variable CD68; being the key point (to exclude LCH) the negativity to langerin (CD207) (Tan SK et al., 2017). Also noteworthy is the non-expression of markers of B/T, CD21, CD23 and CD35 cells (Dalia S et al., 2014).

**DIAGNOSIS** IDCT is frequently misdiagnosed as another dendritic or histiocytic cell neoplasm, with LCH being the most common. Due to the similar histologic findings between these two entities, the clue lies in the lack of langerin (CD207) expression and Birbeck granules in IDCT. Therefore, phenotypic features and the electron microscopy study are the main pillars of IDCT diagnostic.

Neoplastic cells present positivity for CD1a, S100 and CD 68 (variable), and negativity for other dendritic/histiocytic, B and T cell markers. Morphologic findings that could also contribute to LCH exclusion is the absence of eosinophilic infiltration and epidermotropism.

**Cytogenetics**

The identification of ET3V/NCOA2 shows a new molecular landscape in IDCT, not described in other histiocytic neoplasms, which reaffirms that IDCT is a clonal disorder (Davick JJ et al., 2018). ET3V plays a role in last steps of macrophages differentiation as a transcription repressor in the cell cycle; whereas NCOA2 is involved in the activation of some nuclear hormone receptors as a transcription co-activator (Horna P et al., 2017). In addition, molecular alterations are also observed in those IDCT cases that were clonally related with other malignancies, such as trisomies of chromosomes 8 and 21 or IGH/BCL2 translocations (Horna P et al., 2017).

**Genes**

BRAF V600E mutations have been described similarly others histiocytic/dendritic cell neoplasms. Actually, these new molecular aberrations need thorough assessment to determine their impact on the tumor’s biology and therapeutic approaches.

**Treatment**

There is no standardized treatment for IDCT, due to its rarity (Horna P et al., 2017). Surgical resection is usually the therapeutic choice in the majority of cases (Mo X et al., 2015; Dalia S et al., 2014). Psoralen and ultraviolet A therapy (PUVA) have been used with excellent responses, but not more than one year of follow-up does not allow an accurate assessment (Horna P et al., 2017). Chemotherapy treatments are reserved for disseminated cases, and still controversial (Dalia S et al., 2014). Aggressive therapies should be used with caution, since the slow benign clinical course of most of these tumors. Spontaneous remission has also been reported. Clinical trials are recommended since they could determine optimal therapeutic approaches in the future.

**Prognosis**

IDCT is considered an indolent disorder in the vast majority of cases, presenting good responses to surgery (recurrence after resection is extremely rare). Remission without treatment has also been reported. Prognostic factors are not been described usually IDCT (Joo JW et al., 2018).

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