23rd ADIAP INTERNATIONAL CONGRESS
Beirut November 29 - December 3, 2011
Dendritic Cell Associated Diseases: neoplastic and non-neoplastic

SPECIALISED ACCESSORY CELLS OF LYMPHOID TISSUES

Macrophages and histiocytes

Veiled cells

Langerhans cells (LC)

Interdigitating dendritic cell (IDC) of lymph node T-zone

Interstitial DC of parenchymal organs

Plasmacytoid dendritic cells (PDCs)

Follicular dendritic cells (FDC) of lymph node B-cell follicles

Fibroblastic reticular cells (FRCs)
### TABLE I  IMMUNOPHENOTYPE OF ACCESSORY CELLS OF THE IMMUNE RESPONSE

<table>
<thead>
<tr>
<th></th>
<th>BM CD34+ DERIVED</th>
<th>MESENCHYME DERIVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages:</td>
<td>CD14+, CD11c+, CD68+, CD163+</td>
<td>FDC: CD21+, CD23+, CD35+, desmoplakin+, fascin+</td>
</tr>
<tr>
<td>Interstitial DC:</td>
<td>CD1a-, FXIIIa+, CD68+, DCSIGN+</td>
<td>FRC: Muscle actin+, keratin-/+</td>
</tr>
<tr>
<td>Veiled cell:</td>
<td>langerin + (V), CD1a+, S100+</td>
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<td>Langerhans cell:</td>
<td>langerin +, CD1a+, S100+</td>
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<td>IDC:</td>
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<tr>
<td>PDC:</td>
<td>IL3, CD4, CD68+, CD123+, CD303, TCL1, MxA</td>
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</tbody>
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### THE LANGERHANS CELL

- Specialised accessory dendritic cells involved in T-cell immunity
- Origin: Bone Marrow
- Site: Skin & other squamous epithelia eg. cervix, vagina
  oesophagus, respiratory tract, thymus
- Function: dendritic cells involved in antigen capture (endocytosis)
- Morphology: LM: mononucleated cells, folded nuclei dendritic processes
  EM: Birbeck granules. No cell junctions
- Phenotype: MHC Class II
  S100+, CD1a+, Langerin* +
  Immature: CD40+, CD83-, CD86-, DC-LAMP, CD68+, lysozyme+
  Mature: CD40+, CD83+, CD86+, CD208** +, CD68-, lysozyme-
- Adhesion molecules differ between LCH and normal LCs

* CD 207 - lectin involved in → BG
** DC LAMP- lysosome associated membrane protein
INTERDIGITATING DENDRITIC CELL (IDC)

• Specialised accessory Ag presenting dendritic cells

• Origin: Bone Marrow

• Site: paracortex of lymph nodes; T-zones of extra-nodal tissues, BM, thymus

• Function: dendritic cells involved in T-cell immunity
  antigen presentation → T cells

• Morphology: LM: mononucleated cells with rounded to irregular folded nuclei, indistinct cytoplasm;
  EM: Complex interdigitating dendritic processes.
  No Birbeck granules. No cell junctions

• Phenotype: MHC Class II++, S100+, CD1a-, CD68+/-, fascin+

• Prominent in dermatopathic lymphadenopathy
  and in lymph nodes in Sezary syndrome
IDCs in dermatopathic lymphadenopathy

**FOLLICULAR DENDRITIC CELLS (FDC)**

- **Specialised** non-phagocytic Ag. presenting dendritic cells involved in B-cell immunity

- **Origin:** mesenchymal precursor cell - ? Fibroblast precursor (3C8) - ? endothelial cells

- **Function:** Involved in migration, proliferation, cell selection and differentiation into memory B-cells and plasma cells. Direct B-cells to undergo isotype switching and affinity maturation and differentiation by trapping and presenting Ag/immune complexes to B-cells. Only high affinity B-cells survive and escape apoptosis.

- **Site:** GCs of lymph nodes. Most numerous in relation of non-proliferating B-lymphocytes in the light zone. Overall, FDC comprise 1-2% of all GC cells. Also found in non-lymphoid sites with a germinal centre (GC) reaction: eg. synovium in rheumatoid arthritis, gastric mucosa in H. pylori infection, thyroid in Hashimoto’s disease, soft tissues in Kimura’s disease

- **Morphology** LM: Elongate ovoid nuclei, angulated, often in ‘pairs’. Cytoplasm ill defined. Central small to medium sized nucleus. Form polykaryocytes. EM: Long slender interdigitating dendritic processes connected by desmosomes. Processes coated with electron dense protein (IC)

- **Phenotype:** CD21+, CD23+, CD35+, desmoplakin+, fascin+, S100−, CD68−, lysozyme−. Specific markers: mAb to long splice isoform of CD21 (CD21L). 3 other markers also recognise CD21L; DRC-1, KiM4, 7Dk6
Germinal centres (GCs)

MGP

Ki67

FDCs in GCs

CD21
POLYKARYOCYTES

CD21
PLASMACYTOID DENDRITIC CELL (PDCs)

• Specialised monocytes (plasmacytoid monocytes) type 1 interferon α secreting cells

• Origin: Bone marrow

• Previously designated as plasmacytoid T-cells

• Site: recruited to lymphoid tissues and various non-lymphoid sites from circulating monocytes

• Morphology: LM: mononucleated cells with slightly irregular nuclei and scanty well delineated cytoplasm lacking dendritic processes

• Phenotype: CD45+, CD4+, CD68+, CD123+ (interleukin-3 α-chain receptor), BDCA-2/CD303, TCL1, CLA, Mx A (interferon α dependent molecule) CD56-, lysozyme-, MPO-, CD3-

• Prominent in reactive lymphadenopathies, viral infections- eg. HIV, toxoplasmosis, Castleman’s disease and Kikuchi’s disease*
May also rarely be found in association with myeloid neoplasia and some lymphomas, eg. HL and AML

* may possibly be the target cells involved in the necrotic process
PCDs
Reactive lymphadenopathy

CD4
CD3
CD68
Ki67
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CLASSIFICATION OF HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Histiocytic sarcoma

Tumours derived from Langerhans cells
  Langerhans cell histiocytosis
  Langerhans cell sarcoma

Interdigitating cell sarcoma

Follicular dendritic cell sarcoma

Other rare dendritic cell tumours
  Fibroblastic reticular cell tumour
  Indeterminate reticular cell tumour

Disseminated juvenile xanthogranuloma

Blastic plasmacytoid dendritic neoplasm
**LCH**

- Clonal granulomatous disease characterized by accumulation of LCs at various sites*: eg. bone, skin, lung**, BM, lymph nodes, CNS

- Rare disease; about 5/million.

- Lesions solitary or multiple; involve one or more systems

- Any age: mainly children (peak incidence 1-3 years) but adults also

- Familial cases occur but no consistent cytogenetic defect

- Aetiology unknown*:
  - malignant clonal disorder v inflammatory/reactive cytokine expression → eg response to virus v aberrant T cell function → increased survival of LCs*

Course: spontaneous regression, frequent recurrences, progression

* increased survival of LCs due to altered T-cell function (Senechal B et al. 2006)

**Isolated pulmonary LCH associated with smoking

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**TUMOURS OF HISTIOCYTES AND ACCESSORY DENDRITIC CELLS 1**

International Lymphoma Study Group (ILSG). Histopathology 41:1-29. 2002

Study based on 61 cases using IHC

In order of frequency

**LCH**- n=26:
  - typical (LC tumour) = 17
  - atypical (LC sarcoma) = 9

Histiocytic Sarcoma - n=18

FDC tumours - n=13

IDC tumours- n=4

Unclassified – n=4
LANGERHANS CELL HISTIOCYTOSIS (LCH)

Clinical syndrome
Letterer- Siwe disease (L-S D)
Hand- Schuller- Christian disease (H-S-C D)
Eosinophilic granuloma (EG)

Classification Scheme

• Unifocal unisystem disease: eg. - bone (skull, femur, rib, pelvis) lymph node, skin, lung

• Multifocal unisystem disease : H-S-C D; multiple bone sites; skull bones → diabets insipidus

• Multifocal multisystem disease: L-S D - multiple organs (bones, skin liver, spleen, lungs*, lymph nodes, BM)

* Associated with smoking

LANGERHANS CELL HISTIOCYTOSIS

Morphology

LM: LC cells medium to large with distinctive folded nuclei and linear grooves resembling coffee beans.

Atypia minimal. Mitoses variable-usually few
Cytoplasm moderately abundant; lack dendritic processes.

LCs mixed with variable numbers of eosinophils, lymphocytes, macrophages. In lymph nodes, eosinophilic absceses +/- central necrosis

Lymphocytic component comprise many T- cells

Lesions may contain multinucleated cells and giant cell similar to osteoclasts.
Chronic lesions - foamy macrophages, plasma cells; fibrosis

EM: Birbeck granules
**Birbeck Granules (BGs)**

Organelles seen only at EM level

Pentalaminar rods 200-400nm long, 33 nm wide; derive from cell membrane

Terminal flask-like expansions (tennis racket-like)

Sub-domain of the endoplasmic reticulum compartment (ERC)

Identified in LCs and LCH. Express langerin (CD207)

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**LCH: IMMUNOPHENOTYPE**

CD1a +ve, S100 +, CD40+, CD4 +, HLA DR +, vimentin +, CD207+ (langerin) PLAP+*, CD68-/+, lysozyme +/-, CD208+/-

SEMAG6A+**

PI (Ki67) - usually < 10%; may be 25%

Chronic lesions - immature phenotype
Isolated skin lesions - more mature phenotype

Lesions rich in cytokines; eg. IFN γ, CD10

↓ osteolysis, fibrosis

* cf. normal LCs - PLAP –ve.
Also adhesion molecule expression differs between LCH and normal LC

** glycoprotein involved in T- cell immunity
LCH middle ear/temporal bone

S100  CD1a

LCH - lymph node (eosinophilic granuloma)

Sinus involvement → paracortex
Eosinophils +++; eosinophilic abscesses +/- central necrosis
Langerhans Cell Sarcoma: ILSG 2002

9/26 cases of LC tumours

Patients older than LCH

Multi organ involvement

Histology:
- LC cells show pronounced atypia; prominent nucleoli; fewer grooved cells; higher mitotic count-usually>50/10 hpf
- Fewer eosinophils

Immunophenotype: similar to LCH but CD1a + cells focal
- PI (Ki67 10-60%)

Prognosis; aggressive tumour. overall survival 50%
LCH ASSOCIATIONS

HIV lymphadenitis
Lymphomas, especially HL
Leukaemias, myelomonocytic
LCH → LC sarcoma

LCH: PROGNOSTIC FACTORS

- Clinical outcome depends on number of organs affected
- Overall survival is 95% if disease unifocal (75% if 2 organs involved)
- Progression from unifocal lesions to multi-focal disease occurs in 10% of patients
- No correlation of cytological atypia & increased mitotic rate with prognosis (except in LCS)
INTERDIGITATING DENDRITIC CELL (IDC) SARCOMA

Extremely rare neoplasm; single case reports or very small series - 4 cases

Adults predominantly affected (only one paediatric series of 4 cases reported)

Slight male predominance

Sites of involvement variable; LN involvement most common but extranodal sites eg. skin, soft tissues also recorded

Presentation usually with asymptomatic mass; B-symptoms have also been reported and rarely, generalised lymphadenopathy, splenomegaly or hepatomegaly

Prognosis: aggressive clinical course; 50% die from disease and visceral organ involvement - most commonly liver, spleen, kidney, lung

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**IDC SARCOMA**

**Morphology:** Paracortical involvement of lymph nodes with residual follicles
- Spindle to rounded cells → fascicles, whorls and storiform patterns
- Occasionally sheets of round cells
- Nuclei; spindled to ovoid, dispersed chromatin and small to large nucleoli. Occasionally, multinucleated
- Cytoplasm; usually abundant, eosinophilic and borders indistinct
- Cytologic atypia variable. Necrosis not a feature
- Admixed lymphocytes numerous
- Morphologic features may be indistinguishable from FDC sarcoma

**Immunophenotype:** S100+, fascin+, CD68 & lysozyme variable +
- Langerin -, CD1a-, CD21-, CD23-, CD35-
- MPO-, CD34-, CD30-, EMA-
- Admixed small lymphocytes* CD3+ T-cells
- PI (Ki67) 10-20%

**Genetics:** no specific abnormalities currently known
- Ig heavy chain gene and T-cell receptor genes all in germline configuration

* B-cells virtually absent
BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

Aggressive tumour derived from precursor of plasmacytoid dendritic cells (plasmacytoid monocytes – professional type 1 interferon producing cells) with high frequency of skin and bone marrow involvement and leukaemic dissemination

Synonyms: Blastic NK-cell lymphoma; agranular CD4+ natural killer cell leukaemia; CD4+CD56+ haematodermic tumour

Rare haematologic tumour: M/F ratio 3.3:1
Majority of patients elderly (61-67yrs) but can occur at any age

Presentation: Usually asymptomatic solitary or multiple skin lesions
  Regional lymph node involvement common (20%)
  PB and BM involvement minimal; invariable with progressive disease.
  Associated with AML or myelomonocytic leukemia (10-20%)

Prognosis: Aggressive course. Survival 12-14 months despite initial response to multi-agent chemotherapy
  Long lasting remissions reported in sporadic cases. Usually young patients in first remission treated with AML induction therapy followed by ASC transplantation

BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

Morphology: Diffuse infiltrate of medium sized blast cells with slightly irregular nuclei, fine chromatin and one to several small nucleoli.
  Cytoplasm scant and agranular
  Mitoses variable in number
  Angioinvasion and necrosis absent

Skin involvement: sparing of epidermis; extension into subcutis.
  Lymph nodes; leukaemic patter of involvement of inter-follicular areas and medulla.
  BM; varies from mild interstitial infiltrate to massive infiltration. Residual marrow shows dysplasia especially MgK lineage.

Immunophenotype: CD4+, CD43+, CD45+, CD56+, CD68+(50%), TdT+ (33%)
  CD123+, BDCA-2/CD303+, TCL1 CLA+, MxA+
  Other lymphoid and myeloid ass. Ags may be +ve eg. CD7, CD33
  Lysozyme-, MPI-, Granzyme B- & TIA 1 –ve in tissue sections

Genotype: 2/3 of patients → abnormal karyotype
  Specific chromosomal aberrations lacking but 6 complex karyotypes common
  Gene expression profiling and array-based comparative genomic hybridisation have shown certain consistent aberrations
BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

CD4

CD8

CD56
FOLLICULAR DENDRITIC CELL TUMOUR/SARCOMA

Rare tumour

Most commonly present in lymph nodes (2/3 of patients)

Cervical lymph nodes most common site but axillary, mesenteric and retroperitoneallymph nodes also frequently involved

Other sites:
  - Extra nodal lymphoid tissues - tonsil, oral cavity, spleen
  - Extra nodal non-lymphoid tissues – skin, soft tissue, lung, thyroid
    liver, pancreas, GI tract, breast

Adults predominate; mean age 47 (range 14-77)

No sex predominance except liver (F > M)
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FDC Tumour    Histology

Tumours usually well circumscribed

Spindle cells arranged in whorls, fascicles; sometimes storiform pattern

Nuclei usually ovoid: may also be binucleate, multinucleate or assume bizarre forms; usually low mitotic rate

Cytoplasm poorly visualised at LM level  
   EM, long processes connected by desmosomes

Small lymphocytes scattered throughout

Liver and spleen FDC tumours resemble inflammatory pseudotumour

Misdiagnoses without IHC frequent
Mimic carcinoma, thymoma, meningioma, melanoma, inflammatory MFH , lymphomas and other spindle cell tumours- especially IDC sarcoma
FDC tumour/sarcoma

FDC sarcoma: differential diagnoses

- Spindle cell carcinoma
- Malignant melanoma
- Thymoma
- Meningioma
- Inflammatory MFH
- IDC sarcoma
**FDC Tumour: Phenotype**

CD21+, CD23+, CD35+

FDC specific markers +ve: KiM4, K1-FDC1, R4/23

Fascin +ve (non-specific)

Clusterin +ve (highly specific)

Desmoplakin, EMA & HLA DR - +/-ve

S100 & CD68 very variable

CD1a-ve, lysozyme -ve, MPO-ve, CD34-ve, cytokeratins-ve

Ki67 → 1-25%

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**FDC Tumours**

**Aetiology: Unknown**

Although expressing CD21 (EBV receptor), no association with EBV except liver tumours (common in Asians)

**Prognosis variable: 40-50% local recurrences**

Aggressive behaviour: if large tumour > 6cm

- intra – abdominal tumour
- high PI
- significant cytologic atypia

**Metastases:** Lymph nodes, lung and liver most common sites
Diseases with FDC involvement

IMMUNE MEDIATED DISEASES
- Autoimmune diseases: eg. rheumatoid arthritis, Hashimoto’s thyroiditis, H. pylori gastritis
- Castleman’s disease*
- Kimura’s disease*

INFECTIONS:
- Viral diseases eg. HIV*
- Prion diseases eg. Spongiform encephalopathies

LYMPHOMAS
- Follicular lymphoma
- Hodgkin lymphoma
- AIL T cell lymphoma*
- Mantle cell lymphoma

*Associated with increased vascularity

CASTLEMAN’S DISEASE

Hyaline vascular type (HVCD) single node
Plasma cell type (PCCD) group of nodes
Multicentric (MCD) generalised

associated with
- HIV infection
- Kaposi’s sarcoma
- POEMS syndrome
CASTLEMAN’S DISEASE

- A poorly understood lymphoproliferative disorder related to immune dysregulation
- Lymphoid and vascular proliferation with dysfunctional follicles
- Prominance of PDCs around vessels
- Usually a polyclonal non-neoplastic disorder
- PCCD associated with generalised lymphadenopathy and systemic symptoms and immunological disorders. May rarely progress to a BCL (usually plasmacytic)
- FDC sarcoma seen in conjunction with CD (10-20% cases) or follows yrs later. Evidence that HVCD is a precursor of FDC sarcoma
- >95% of MCD cases occur in HIV+ patients
- MCD may:
  - Be associated with HHV8 (KSHV) and KS. PEL may also co-exist.
  - HHV8 encodes a viral IL 6; IL 6 induces B-cell proliferation and angiogenesis.
  - vIL 6 is expressed in cells around GCS which are monotypic for lambda light chains and may undergo monoclonal expansion to plasmablastic lymphoma.

CASTLEMAN’S DISEASE  HYALINE VASCULAR (HV) TYPE

Masson trichrome
HVCD
vascularity

CD34

Castleman’s disease
plasma cell (PCCD)
Plasmacytoid dendritic cells
FDCs in CASTLEMAN’S DISEASE

FDC are hyperplastic; express CD21 CD35

Dysplastic FDCs in HV CD express
   ICAM-1 VCAM-1 ELAM-1 (Ruco et al 1991)

Factor VIII, Ulex, laminin +ve in PC CD (Hall et al 1989)

Associated with KS and other vascular tumours

Associated with HHV8+ve pl.blasts in MC CD (Du et al 2001)

Clonal cytogenic aberration of chr.12 (Cokelaere et al 2002)

EGFR +ve (Sun et al. 2003)
HIV ASSOCIATED LYMPHADENITIS

• Follicular hyperplasia; follicular lysis and disrupted FDC network

• Hyperplasia of FDCs & formation of polykaryocytes

• Increased vascularity

• Prominance of Ig secreting plasma cells

• CD-like changes

• Trapping of HIV on FDC processes as highly infectious HIV IC; no budding of HIV indicative of active infection of FDC

• HIV infection of target T cells requires CD4 R and CXCR4- a chemokine receptor expressed only by T-cells in the GC

• FDCs increase CXCR4 expression of T- cells and susceptibility to HIV infection
HIV lymphadenitis
FDC hyperplasia

Masson trichrome
HIV lymphadenitis plasma cell in GCs
FDC and HIV INFECTION

Functional aspects:
FDCs- trapped Ag (unprocessed) persists for many months and maintains long term memory IgG and IgE responses to soluble Ag.

FDCs are reservoir for virus and play key role in CD4 infection

Virus is trapped on FDC dendritic processes as highly infectious immune complexes (IC)

FDCs AND LYMPHOMAS

FDCs crucial to development and differentiation of B cells

Specialised CXCL13+ve T-cells in GCs interact with FDCs

FDCs contribute to lymphomagenesis by preventing apoptosis and proliferation of transformed B-cells

Activated FDCs, T-cells, B cells may affect genetic instability and → lymphoma

FL, MCL & HL considered to derive from GCs

Evidence now that T-cells in AIL T- cell lymphoma are GC derived
LYMPHOMAS WITH FDC INVOLEMENT

Follicular lymphoma (FL)
Mantle cell lymphoma (MCL)
Angioimmunoblastic T-cell lymphoma (AILT)
Hodgkin lymphoma (HL)
FOLLICULAR LYMPHOMA (FL)

Disturbance in FDC/B cell interactions in FL

• In FL, adhesion of B cells to FDC is via adhesion pathways LFA-1/ICAM-1 VLA-4/VCAM-1.
  B cells lacking VLA-4, LFA-1 α & β (CD11a, CD18) and ICAM-1 could result in detachment of B cells and progression to a diffuse growth pattern (Petrasch et al 1992, 1994)

• Absent or reduced FDC fascin expression in FL (Said et al 1998)

• Dense CD21 +ve FDC networks usually present in low grade FL and rare in high grade FL. Loss CD21+ve networks associated with progression to high grade FL (Shiozawa et al 2003).

ANGIOIMMUNOBLASTIC T CELL LYMPHOMA
AILT and FDC

FDCs - Key component of stromal-vascular change
Diagnostic aid to diagnosis

FDC proliferation pattern changes with progression of disease

CD10 expressed by T-cells in 90-100% cases

CD10/ CXCL13* co-expression by AILT T-cells and CG T-cell suggests origin of AILT from GC FDC associated T-cells

*also expressed by FDC


*also expressed by FDC
Mantle cell lymphoma

- CD5
- Cyclin D1
- CD21
- MCL - diffuse

Normal / activated
Mantle cell lymphoma (B)

Cyclin D1
CD5
CD21
MCL and FDC

Study of 94 patients:

FDC always present: in residual follicles
  in colonised follicles
  as residual networks

Diffuse pattern worse prognosis than nodular pattern
  (regardless of whether blastoid variant)

Schrader c et al. Virchows Arch 448: 151-159, 2006
HODGKIN LYMPHOMA

PROGNOSIS AND FDC STATUS:

Best prognosis - HL NLP

Intermediate prognosis - HL NS and MC with FDC in neoplastic areas

Absence of FDC in neoplastic areas - unfavourable prognosis

Alavaikko et al 1994

DIAGNOSIS:

Presence of FDC useful in separating HL NLP from T/HRBCL

Boudova et al 2003
FDCs AND LYMPHOMAS

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DISEASE IS OF OLD AND NOTHING ABOUT IT HAS CHANGED

IT IS WE WHO CHANGE WHEN WE LEARN TO RECOGNISE WHAT FORMERLY WAS IMPERCEPTIBLE

Jean Marie Charcot 1825-1893
Phycisian, Salpêtrière Hospital, Paris