Unique Cytoplasmic Pattern of Cyclin D1 Immunostaining Distinguishes ECD with MAPK-Pathway Mutations from Reactive Histiocytic Infiltrates

Alma R. Oskarsdottir[1], Aishwarya Ravindran[2], Matthew J. Koster[1], Jithma P. Abeykoon[1], Nora Bennani[1], Mithun V. Shah[1], Gaurav Goyal[2], Ronald S. Go[1], Karen L. Rech[1]

[1] Mayo Clinic, Rochester, MN

[2] University of Alabama at Birmingham, Birmingham, AL

Presenter: Alma R. Oskarsdottir, M.D.

Disclosures

None

Erdheim-Chester Disease

Xanthogranulomatous disease

Positive: CD68, CD163, Factor XIIIa

Negative: CD1a, Langerin

S100 rarely expressed

Activating MAPK-pathway genetic alterations common

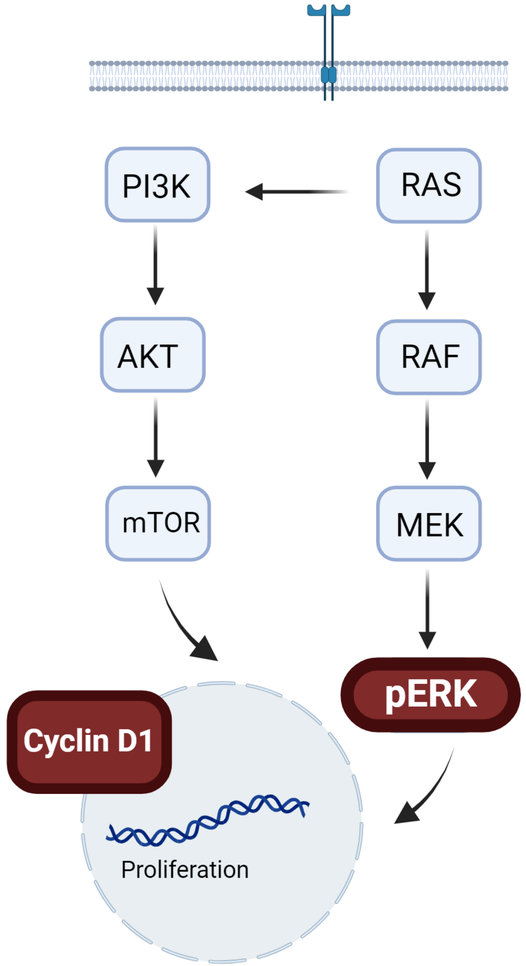
Phosphorylation of ERK and overexpression of downstream proteins

Cyclin D1

Integral part of cell cycle regulation, located in nucleus and cytoplasm

Cyclin D1 overexpression reported in other histiocytic neoplasms

Langerhans Cell Histiocytosis, Rosai-Dorfman Disease



Created with biorender.com

Methods

Archive search for **ECD cases** and **controls**

Control cases including: Idiopathic retroperitoneal fibrosis, cutaneous xanthogranuloma, IgG4-related disease, xanthogranulomatous pyelonephritis, fat necrosis, fibrous dysplasia

Review of morphology and immunophenotype in all cases and controls

CD163, Factor XIIIa, BRAF V600E, Cyclin D1, pERK

Review of genetic studies and correlation with genetic alterations

Created with biorender.com

Results

Patient Characteristics – ECD cases

36

25 11

Median age: 60 years (19-81)

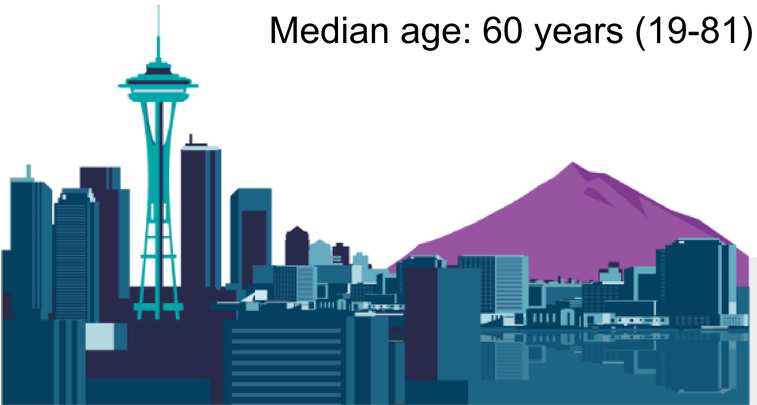
Biopsy sites

- Perinephric/retroperitoneum (9)
- Skin (9)
- Central nervous system (5)
- Heart (4)
- Bone (3)
- Other (6)

Genetic alterations

- MAPK-pathway alterations (31)
  - BRAF V600E (16)
  - Other BRAF mutation (2)
  - BRAF fusion (4)
  - MAP2K1 mutation (8)
  - NRAS mutation (1)
- CSF1R mutation (2)
- FLT3-MEF2C fusion (1)
- No alterations detected (2)

Created with biorender.com



Results

Is there consistent pattern of cyclin D1 expression in ECD cases, and how does it correlate with genetic alterations?

Nuclear + Cytoplasmic Expression

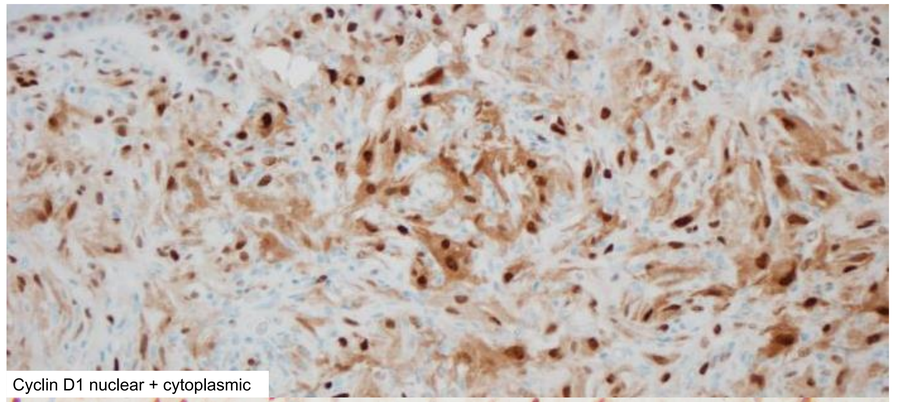
30/36 (83%) ECD Cases

28/31 (90%) MAPK-pathway altered

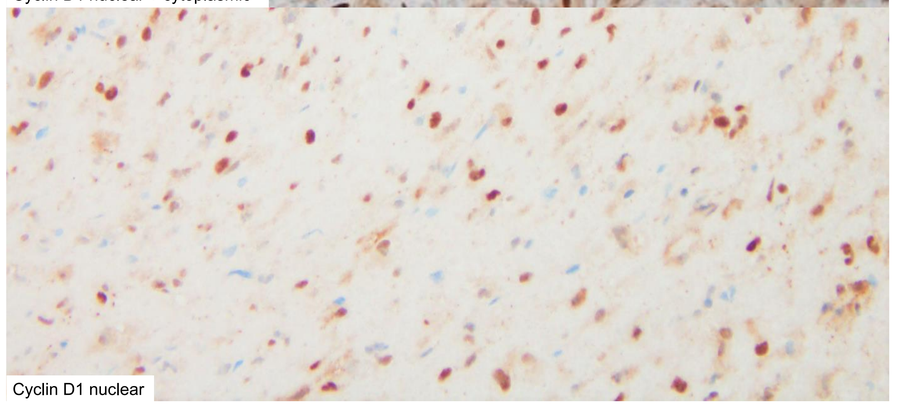
2/2 (100%) No mutation

Nuclear Expression

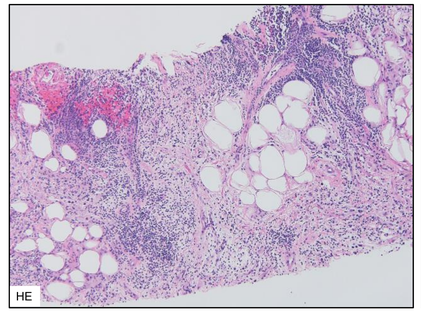
2/2 (100%) CSF1R mutated



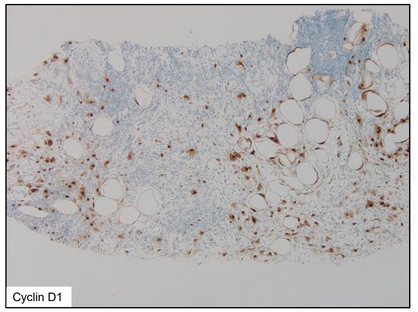
Cyclin D1 nuclear + cytoplasmic



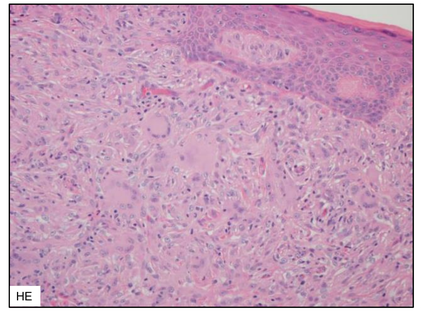
Cyclin D1 nuclear



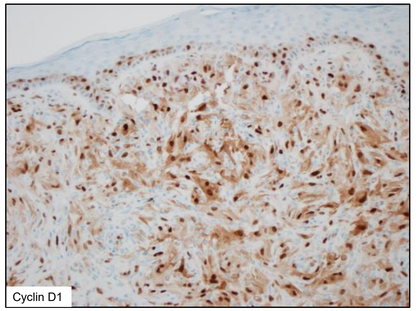
HE



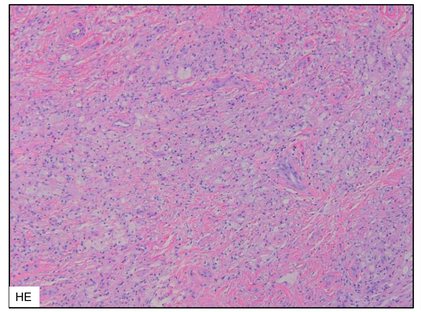
Cyclin D1



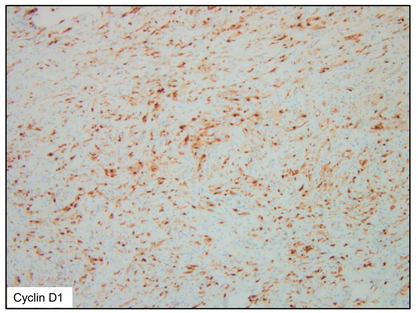
HE



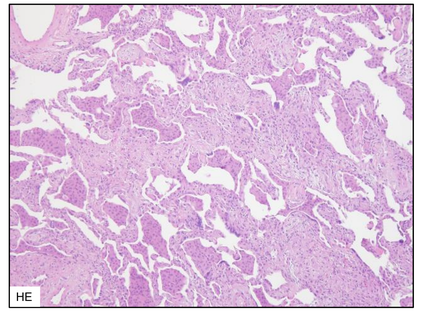
Cyclin D1



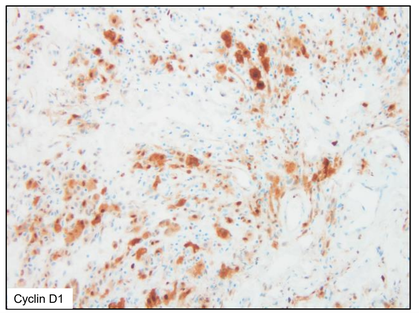
HE



Cyclin D1



HE



Cyclin D1

Results

How does cyclin D1 expression compare to pERK expression in ECD?

Cyclin D1 (Nuclear + Cytoplasmic)

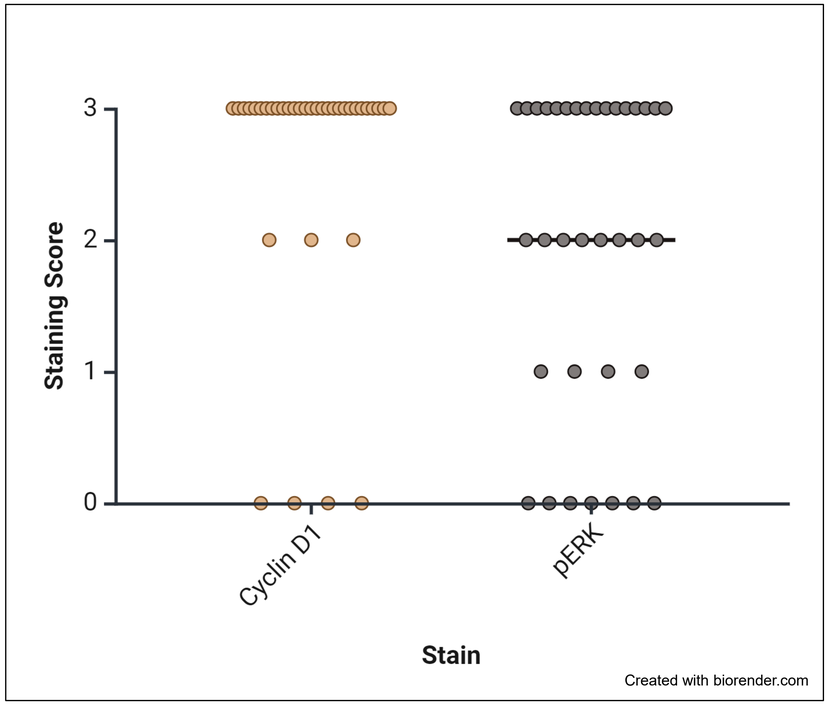
30/36 (83%) ECD cases

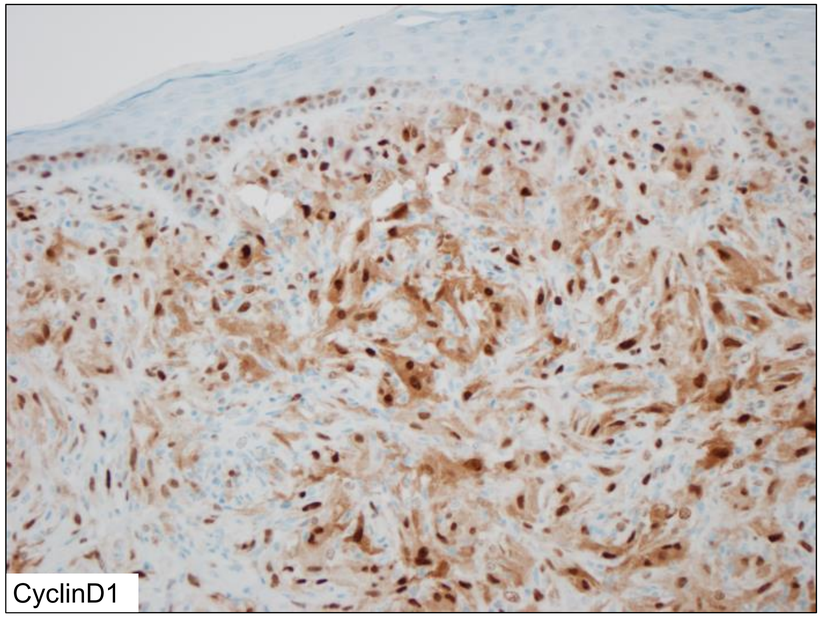
24/36 (67%) Diffuse & Strong (2-3)

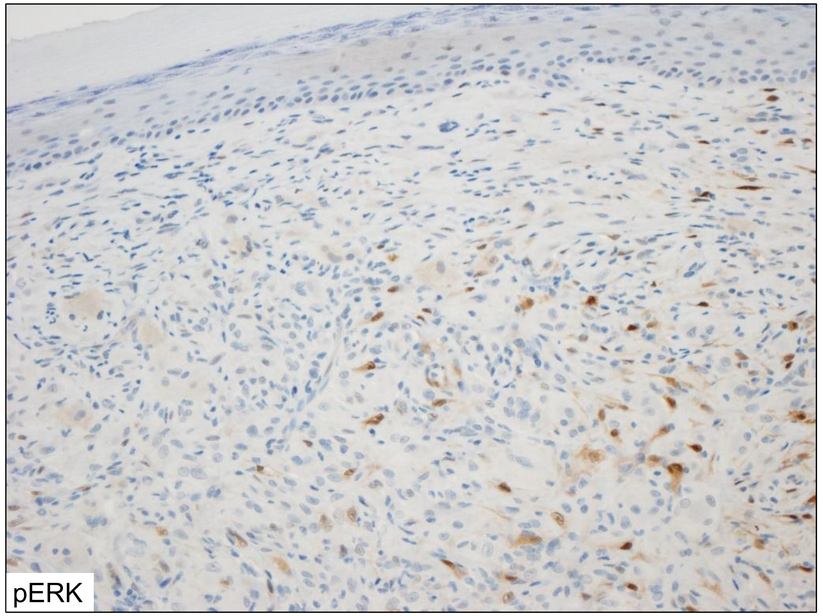
pERK (Nuclear + Cytoplasmic)

28/35 (80%) ECD cases

18/35 (51%) Diffuse & Strong (2-3)







Results

Is there consistent cyclin D1 or pERK expression in benign/reactive histiocytic infiltrates?

Control cases

Idiopathic retroperitoneal fibrosis (10)

Benign xanthogranuloma (3)

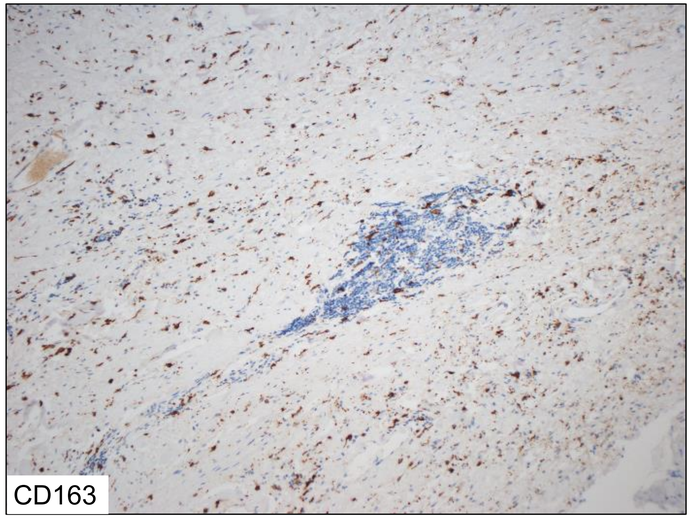
Orbital xanthogranuloma (2)

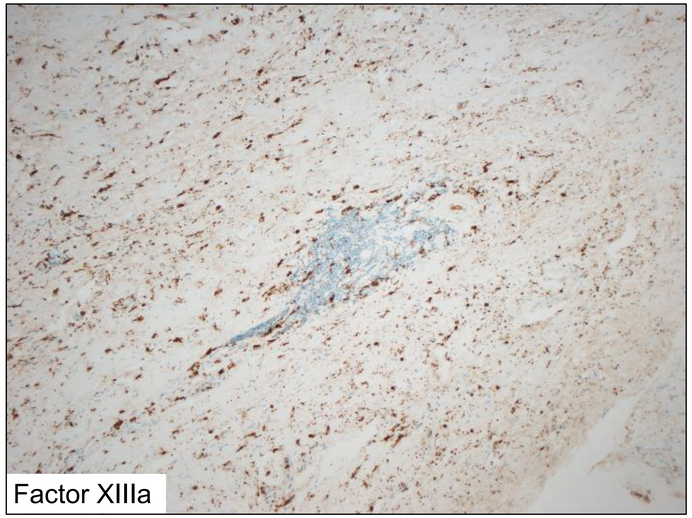
IgG4-related disease (1)

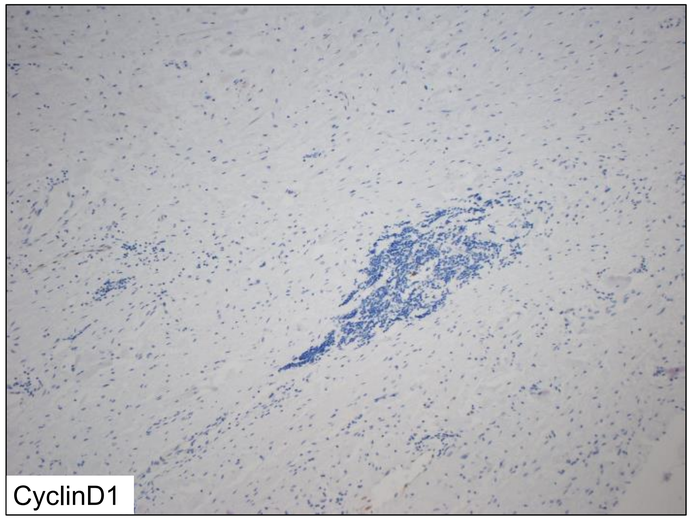
Xanthogranulomatous pyelonephritis (1)

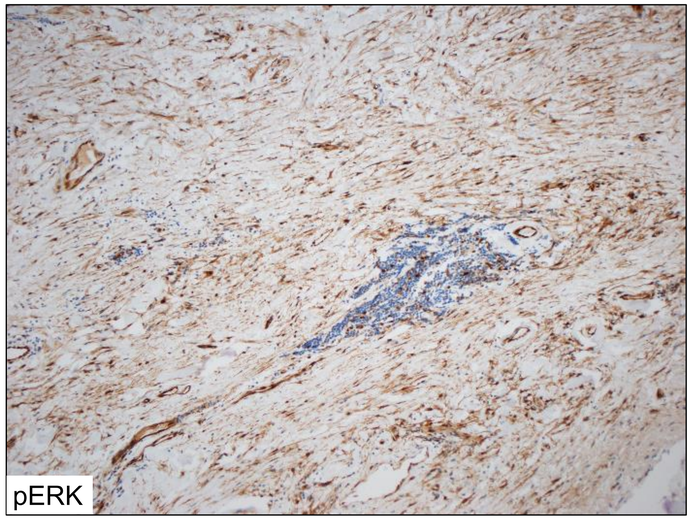
Fibrous dysplasia (1)

Post-chemotherapy histiocytic pseudotumor (1)









Conclusions

Consistent overexpression of cyclin D1 in nucleus and cytoplasm of MAPK-pathway altered ECD cases

Unique pattern that helps distinguish ECD from reactive histiocytic infiltrates

Results should always be correlated with clinical presentation, radiologic features and genetic studies

Cyclin D1 has different functions depending on its location in the nucleus or cytoplasm
- Cytoplasmic location in ECD may give insight into its role in pathogenesis

For Additional Information

oskarsdottir.alma@mayo.edu