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Disordini linfoproliferativi e immunodeficienze primitive: le possibili insidie diagnostiche. Novità Terapeutiche III

KEY MESSAGES

SLIDE 2

- Inborn Errors of Immunity (IEIs) are rare disorders of genetic origin, generally monogenic
- The last IUIS classification shows 10 categories and 485 different monogenic disorders
- About 129 genetic causes are associated with Primary Immune Regulatory Disorders (PIRDs): non malignant lymphoproliferation accounts for one of the most represented phenotypes

SLIDE 3

- Non malignant lymphoprolieration: proliferating (and/or persistent) clonal or polyclonal lymphoid cells that may arise as aberrant responses to immune stimuli or represent intrinsic immune dysregulation
- Clinically and genetically heterogeneous: diagnostic paths are challenging
- Increased predisposition toward developing hematopoietic malignancies, specifically lymphoma
- diagnostic and therapeutic paths forward for patients with evidence of lymphoproliferation remain **poorly defined**

SLIDE 4

- The new standardized nomenclature builds on an integrated approach to diagnosis that combines all relevant data into a reporting system as follows:
  1) Histological diagnosis according to accepted criteria and terminology; 2) Presence or absence of one or more oncogenic virus(es); and 3) The clinical setting/immunodeficiency background
- Patients with IEI may develop distinctive types of lymphoid proliferations unique to particular IEI

SLIDE 5

- LPDs diagnosis is challenging
- Difficulties both in the clinical assessment of the patient, histological classification and in the identification of pathogenic mechanisms to differentiate LPDs
- Nonmalignant lymphoproliferative disorders (LPDs) often underly an Inborn Error of Immunity **(IEI) ->** mechanism-based therapy strategy

SLIDE 6

- Poor data and often only isolated case reports describe in detail the features of limphoproliferative disorders associated to IEIs
- Common histopathologic findings have been described, often aspecific, sometimes lymph nodes histologic alterations may be informative for some specific IEIs

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KEY MESSAGES

SLIDE 7-8-9

- Examples of histopathological features of node architecture and IEIs
- SLIDE 9: Activated PI3K-kinase Delta Syndrome (APDS) – IEI due to mutation in the PI3K complex involving the PI3K-Akt-mTOR pathway

SLIDE 10

- APDS lymph node: Effacement of lymph node architecture, with vague nodular growth pattern
- **Lymphadenopathy** is **common** in APDS patients and the evaluation of this is challenging due to the **broad differential**
- Patients may **have lymphoid hyperplasia** in MALT-associated sites making it **difficult** to **distinguish** between **benign** and **malignant proliferations**.

SLIDE 11

- APDS is caused by activating mutations in phosphoionositide 3-kinase delta (PI3Kδ) which is a heterodimer present predominantly in leukocytes and plays an important role in leukocyte proliferation, activation and survival. PI3KCD gain of function mutation, PIK3R1 loss of function mutations.
- Patients with APDS also experience lymphoid hyperplasia, autoimmunity, increased susceptibility to herpes viruses, especially Epstein-Barr virus and cytomegalovirus
- The increase in B-cell proliferation in combination with a reduced immune system may contribute to the development of B-cell lymphoma.

SLIDE 12

- Activated phosphoionositide-3 kinase delta syndrome (APDS): from genetics to therapy
- Tailored therapy targeting PI3K-AKT-mTOR pathway (clinical trials.gov)

SLIDE 13

- case report of a patient followed in Immunology, IRCCS S.Orsola Bologna: Activating mutation of PIK3R1 was found in a 30-year-old woman with refractory systemic lupus erythematosus, autoimmune cytopenia, and diffuse lymphoproliferation
- 20-year-old: Hodgkin's lymphoma, although atypical aspects emerged: FDG-PET/CT
- 21 year-old: refractory systemic lupus erythematosus
- One year after APDS2 diagnosis and rapamycin treatment, FDG-PET/CT confirmed remission of lymphoproliferation, showing a complete metabolic normalization of all sites
- the presence of atypical patterns and unusual metabolic uptake at FDG-PET/TC should be interpreted as a red flag for the need of an early immunological evaluation, especially in patients with other features of immune dysregulation to avoid misdiagnosis and diagnostic delay.

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KEY MESSAGES

SLIDE 14

- LPDs evaluation and treatment
  - ◊ Integrated diagnostic workup (histopathology, oncogenic viruses, immunological and genetic background)
  - ◊ LPDs **->** specific immunological and functional tests + EBV exclusion **->** tissue biopsy **->** genetic evaluation **->** observe/support or targeted therapy or HSCT

SLIDE 15

- Patients with IEI may develop distinctive and heterogeneous types of lymphoid proliferations unique to the particular IEI -> diagnosis is often challenging
- The types and frequency of these proliferations are largely dependent on the immune dysregulation conferred by the **germline aberration** underlying a respective IEI
- **Clinical** history, **immunological** and **histological** characterization are critical for establishing a **prompt diagnosis** of an underlying IEI
- LPDs in the context of IEI may take advantage from **mechanism-based therapies** -> urgent need of specific diagnostic and treatment strategy path to **prevent delayed** diagnosis