

CIS 2016 School in Primary Immunodeficiency Diseases

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Late onset combined immunodeficiency of unknown genetic origin presenting with persistent EBV viremia, colitis and pulmonary Aspergillosis

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Patient



Clinical Hallmarks

- At 13 years of age, 3 months after an episode of infectious mononucleosis diagnosis of ulcerative colitis initially treated with Methylprednisolone and Mesalazine and then with Azathioprin. After 10 days of steroid treatment:
 - Pulmonary Aspergillosis → treated with Voriconazole for 9 months
 - Pneumocystis Carinii infection → treated with Cotrimoxazole the shifted to prophylactic dosage
 - Persistent EBV infection (24 months)
- Dysmorphic features (long narrow face, thin upper lip, valgus knee, reduced mobility of upper limb joints)
- Short Stature
- Iron deficiency anemia

Family History: not contributory



1. What clinical features suggest an immunodeficiency?
2. Are Methylprednisolone and Mesalazine implicated in the pathogenesis of such clinical manifestations?
3. What is your differential diagnosis?
4. What laboratory examinations would you like?



Laboratory examinations

(performed after a four-month off therapy period)

| | Absolute number (cells/ μ L) | Relative Number (%) | Reference value* (cells/ μ L) | Reference value* (%) |
|--------------------------|-------------------------------------|------------------------|--------------------------------------|-------------------------|
| Total Lymphocyte | 500-1180 | - | 1000-5300 | |
| CD3 | 1014/979 | 83/89 | 800-3500 | 60-78 |
| CD3CD4 | 366[#]/176 | 26/16 | 400-2100 | 30-48 |
| CD3CD8 | 648 [#] /583 | 46/53 | 200-1200 | 14-37 |
| CD3HLADR | - | 25 | - | 1-8 |
| CD19 | 22 | 2 | 200-600 | 6-20 |
| CD56 | 99 | 9 | 100-1200 | 5-27 |
| CD4CD45Ra | | 44 | | |
| CD4CD45RO | | 56 | | |
| CD8CD45Ra | | 80 | | |
| CD8CD45RO | | 20 | | |
| CD4-CD8- $\alpha\beta$ + | | 0.4 | | |
| CD4/CD8 | 0.32 | | | 0.9-3.4 |

| | Serum levels (mg/dL) | Reference value |
|----------------------|----------------------|-----------------|
| IgG | 329 | 604-1909 |
| IgA | 64 | 61-301 |
| IgM | 50.7 | 59-297 |
| HbsAb | Absent | |
| Allohaemoagglutinins | Absent (Group AB) | |



| Degranulation Assay | 50% of the healthy control |
|--|----------------------------|
| NBT test | Normal |
| Proliferative response to mitogens (PHA, PWK and ConA) | Normal |

* Dalla Villa et Al, Medico e Bambino, 2015

1. Which immunodeficiency diagnosis category do the clinical and laboratory findings suggest?
2. Which genes may be implicated in the pathogenesis of this clinical phenotype?

Targeted NGS

| | | |
|---------|---------|-------------|
| ADA | DOCK8 | IL1RN |
| AP3B1 | ERCC2 | IL2RG |
| ATM | ERCC3 | JAK3 |
| BLM | FERMT3 | LIG4 |
| BLOC1S6 | FOXN1 | LYST → WT |
| BTK | FOXP3 | MPV17 |
| CD19 | G6PC3 | MYD88 |
| CD247 | GTF2H5 | NHEJ1 |
| CD3D | ICOS | ORAI1 |
| CD3E | IFNGR1 | PRF1 → WT |
| CD3G | IFNGR2 | RAB27A → WT |
| CD40LG | IKBKG | RAG1 |
| CFP | IL12B | RAG2 |
| DCLRE1C | IL12RB1 | RMRP |

Sanger sequencing

PI3KCD → WT
PI3KR1 → WT
LRBA → Ongoing
BIRC4 → WT

SH2D1A → WT

SLC35C1

SP110

STAT1

STIM1

STX11 → WT

Trio Whole Exome Sequencing → ongoing



During the follow up...

After the resolution of EBV infection (negative serum EBV-DNA)

| | Absolute number (cells/ μ L) | Relative Number (%) | Reference value* (cells/ μ L) | Reference value* (%) |
|------------------|----------------------------------|---------------------|-----------------------------------|----------------------|
| Total Lymphocyte | 1360 | - | 1000-5300 | |
| CD3 | 1047 | 77 | 800-3500 | 60-78 |
| CD3CD4 | 408 | 30 | 400-2100 | 30-48 |
| CD3CD8 | 503 | 37 | 200-1200 | 14-37 |
| CD19 | 81.6 | 6 | 200-600 | 6-20 |
| CD56 | 99 | 8 | 100-1200 | 5-27 |
| CD4/CD8 | 0.81 | | | 0.9-3.4 |

| | Serum levels (mg/dL) | Reference value |
|----------------------|----------------------|-----------------|
| IgG | 1080 | 604-1909 |
| IgA | 65.9 | 61-301 |
| IgM | 62.2 | 59-297 |
| HbsAb | Absent | |
| Allohaemoagglutinins | Absent (Group AB) | |



* Dalla Villa et Al, Medico e Bambino, 2015

How would you explain the improvement of the clinical and lab phenotype after the resolution of the EBV infection ?

Is this all due to immune suppressive therapy?

What would you do now?

The image features a central blue circle surrounded by several concentric red rings, creating a tunnel-like or target-like effect. The text "To be continued..." is written in a white, cursive font, centered over the blue circle and extending across the red rings.

To be continued...