Therapeutic management in a boy with XL-CGD complicated by invasive aspergillosis.

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Polish Primary Immunodeficiency Registry

Currently it includes 1021 patients.
44 of them were given the diagnosis of chronic granulomatous disease.

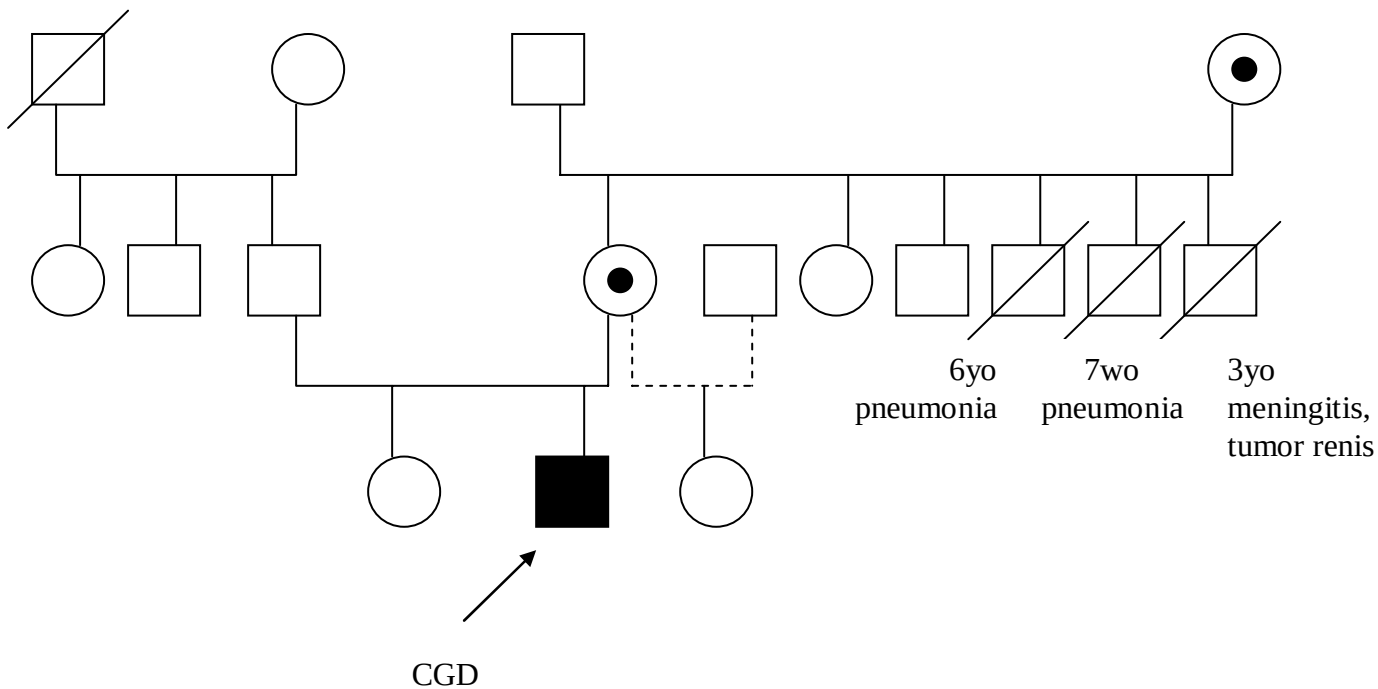
During 26- year- experience,
only 11 of our patients afflicted with CGD, developed invasive aspergillosis (IA) **despite antifungal prophylaxis.**

Case report

- 3 y. o. boy with medical history including recurrent lymphadenitis and pneumonia, otitis media, staphylococcal sepsis, tonsilitis, stomatitis and the suspicion of pulmonary tuberculosis.
- The diagnosis of CGD based on ESID criteria:

- NBT slide test 0% (at the age of 29 mo)
- positive for CGD family history

The pedigree



Clinical presentation

At the admittance:

- 6- week- lasting fever
- dyspnoe + tachycardia
- cough + vomitting
- chest pain
- loss of weight
- asymmetry of the precordial area
- generalised lymphadenopathy + hepatomegaly

Diagnostics

- Elevated- CRP, BSR and WBC
- **The diagnosis of IPA was confirmed by:**

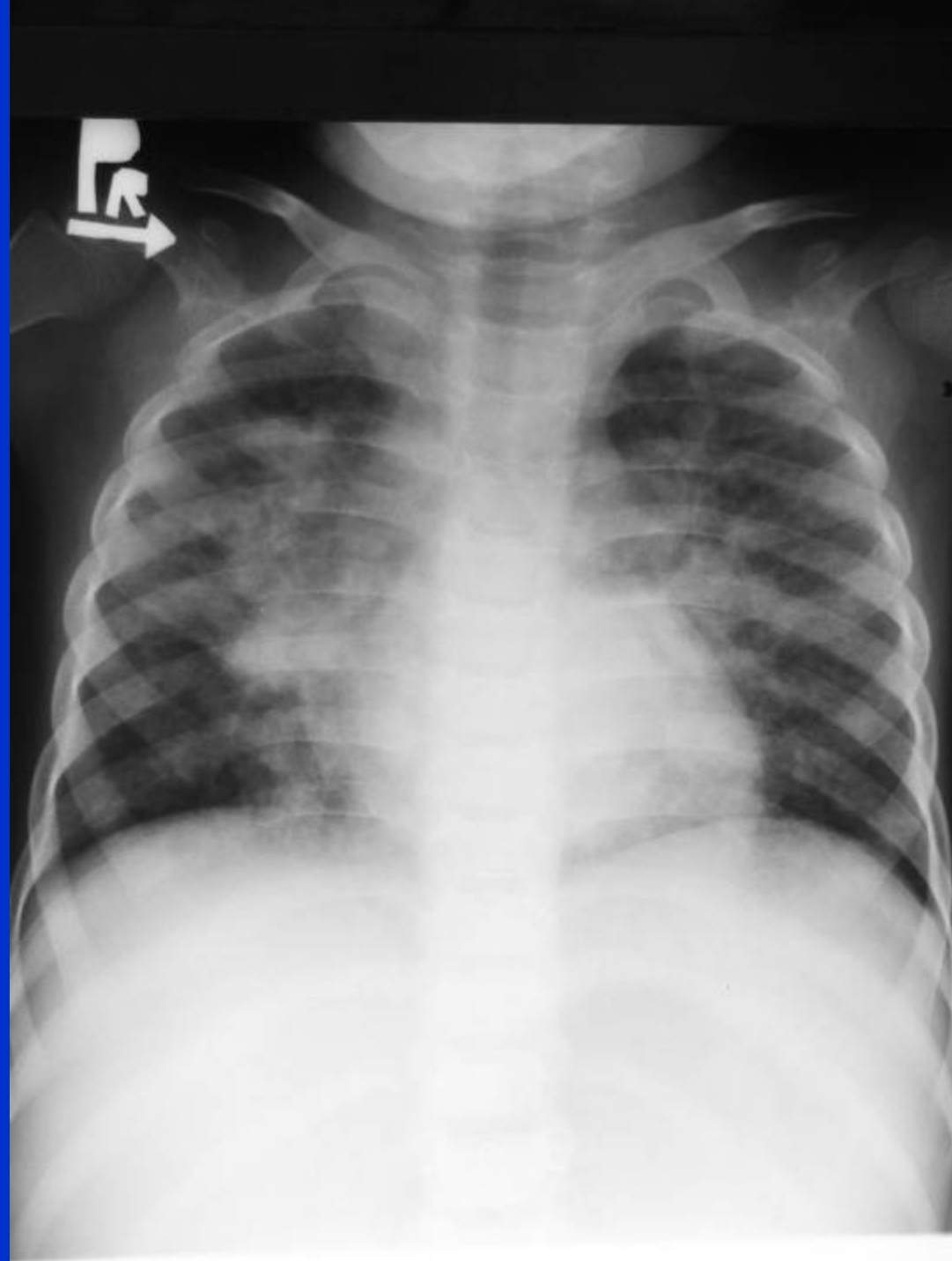
- chest HRCT scan
- positive for Aspergillus:
  - bronchoalveolar fluid culture
  - histopathology
  - DNA / PCR serum examination

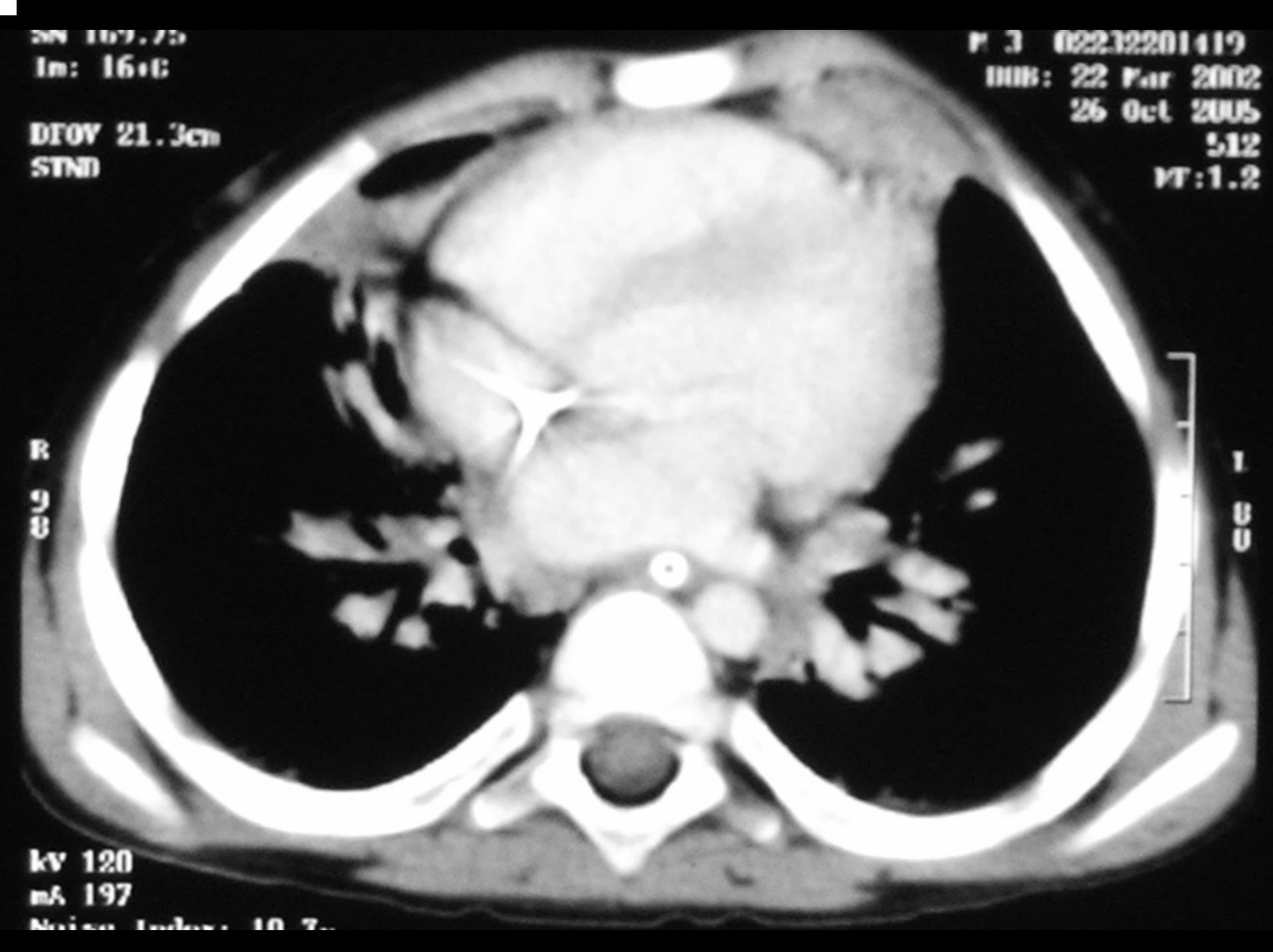
- Interestingly- Aspergillus galactomannan ELISA was negative !

Chest X- ray before antifungal treatment

- bilateral massive pulmonary infiltrates

- enlarged lymphnodes in mediastinum

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Therapeutic management

- monotherapy with Voriconazole

  antifungal drug- excellently penetrating to either lungs or central nervous system

- no improvement achieved despite

  12- day- treatment

Therapeutic management

- **Caspofungin** was added.
- 5- day- treatment:

  improved general condition

  a little radiologic regression

  decreased CRP, BSR, WBC
- **Voriconasole ceasation-** due to:

  acute haematuria + anuria

  acute renal inssuficiency

Therapeutic management

- During Caspofungin monotherapy clinical (fever, dyspnoe) and radiological worsening was observed.
- CNS fluid examination- to exclude CNS involvement
- DNA of Aspergillus fumigatus- detected in CNSF by PCR

Therapeutic management

- general examination of CNSF- negative
- MRI of brain revealed no pathologic aberrations typical of IA
- **liposomal Ampho B** (penetrating through brain/blood barrier) was added.
- double- drug- treatment conducted for 16 days
- the recurrence of fever + worsening in HRCT chest scan was observed

Therapeutic management

- Caspofungin was stopped.
- **Liposomal Amphotericin B**
  - in a higher dose up to 7 mg/kg
  - continued for 76 days
  - gradual clinical, radiological and laboratory improvement
- Next the boy was put on **oral Voriconasole** at the dose of 4 mg/kg b.d.

Therapeutic management

- no important adverse events of Voriconazole
- only mild and typical problems, like:
  visual disturbances
  redish rash (hands + feet)

After 3 months the dose of Voriconazole had to be increased (to 7 mg/kg b.d.) due to worsening of laboratory and imaging tests.

Therapeutic management

- 3rd HRCT of thoracic cage performed after 7 mo of Voriconasole treatment
- It revealed:
  - treatment resistant 2 masses- precordial area
  - pulmonary fibrosis
  - there were neither small nodules nor enlarged lymphnodes

Therapeutic management

- The surgical treatment was performed.
- Histo- pathological examination confirmed granulomata infiltrated by Aspergillus fumigatus.

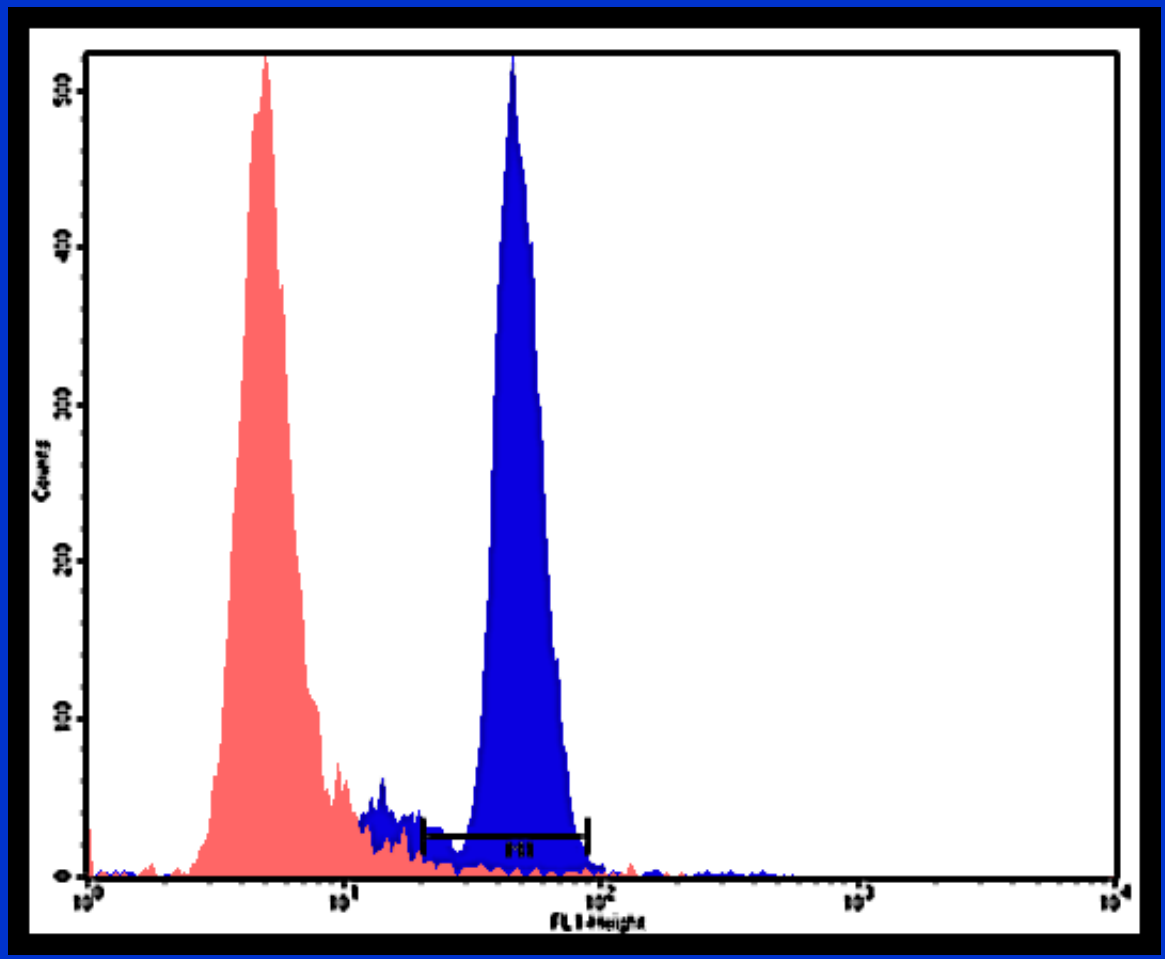
Therapeutic management

- **Succesful surgery**, followed by oral Voriconasole treatment, let us prepare the child to MUD- HSCT.
- **Only after 2nd HSCT procedure** the complete donor's chimerism and full reconstitution of granulocytic series was achieved.
- **Immunologic improvement** was confirmed by normal either NBT slide test or DHR (respiratory burst).

Current flow cytometry analysis of PB

• CD 45		3632 cells /ml
• CD3+CD45+	86.5 %	3142
• CD3+CD8+	73.4 %	2666
• CD3+CD4+	10.4 %	376
• CD16+56+	8.2 %	299
• CD19+	3.7 %	134
• CD4+/CD8+	0.1	

Normal Respiratory Burst in FC



Conclusions

- Aspergillus sp. infection- an arising and life-threatening- problem in CGD- patients

  needs long- term and high- dose antifungal treatment.
- Voriconasole seems to be the drug of choice in CGD complicated by IA.
- In patients afflicted with CGD the complete resolution of IA may require HSCT.

Thank you for your attention!