CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Best Western Hotel Madison
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LINFOMA IN IMMUNODEFICIENZA CONGENITA

FRANCESCA GAIA ROSSI DARDANONI
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano

Disclosures of Francesca Gaia Rossi Dardanoni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda						X	
J&J						X	X
Incyte						X	X
Pierre Fabre						X	X
Kyte Gilead						X	X
Regeneron							X

2014	2016	2018	2020	2022	2024

30 year-old male patient presented to hospital in January 2014

Symptoms:
- Oral bleeding
- Nosebleed

Patient history:
- recurrent sinusitis
- tympanic perforation for streptococcal infection

Current medications:
Not chronic therapy

Allergic to Ceftazidime

Patient evaluation:
- Petechiae
- Mucosal bleeding

CBC:
- Hb 11 g/dl
- MCV 80 fL
- *PLT 10.000/mm^3*
- WBC 2500/mm^3
- N 1100/mm^3

DIAGNOSTIC WORK UP

1. Viral PCR for EBV, CMV, HIV and Parvovirus
2. H. pylori
3. Anti-thyroid antibodies and thyroid function
4. Pregnancy test
5. Antinuclear antibodies
6. Antiplatelet antibodies (poor sensitivity)
7. Anti-PMNs antibodies
8. Bone marrow examination (in selected patients)
9. Abdominal ultrasound

1. PCR CMV, HIV and Parvovirus: negative, **PCR for EBV: 1424 copies/ml**
2. H. pylori: negative
3. Thryoid function: normal

5. ANA: negative
6. **Antiplatelet antibodies positive**
7. **Anti-PMNs antibodies positive**
8. **BOM: irregular cellularity with hypocellular area and dyserythropoiesis, increased number of megakaryocytes with dysplastic morphology and some immature megakaryocytes**
9. Abdominal ultrasound: negative, no splenomegaly.

Idyopathic Thrombotyc Purpura

What type of first line therapy? Which sequencing?

1. **PLT transfusion** → *recommended in case of bleeding, but not enough on its own*

2. **Steroids p.o. (1 mg/kg/day)** → *mandatory if platelet count < 20-30000/mmc and bleeding grade ≥ 2*
3. **Steroids e.v. and IVIG** → *recommended in patients requiring a quicker response due to severe bleeding or showing no response in the first days*

4. **Rituximab** → *not in first line*

5. **Eltrombopag or other TPO mimetics** → *not in first line*

2014	2015	2016	2017	2018	2019

Initial Treatment

Started prednisone 1 mg/kg/day

No response after few days

Started dexamethasone 40 mg and IVIG 0.4 gr/kg

Partial response

May 2015

- ITP relapse with mucosal bleeding
- Admitted to hospital with PLT 6.000/mm3

Started Rituximab 375 mg/m^2 weekly for 4 weeks

Partial response

Early 2016

After few months, new ITP relapse treated with IVIG with good response
But one month later, PLTs dropped to 25.000/mm^3

Started eltrombopag 50 mg/day

2019	**2020**	**2021**	**2022**	**2023**	**2024**

Reassesment

In the following years frequent platelet count oscillation.

BOM: *cellularity 20-30%* and dyserythropoiesis.

Abdominal ultrasound: negative, no splenomegaly

August 2019

He was admitted to hospital for fever and diarrhea.

CBC
- Hb 11 g/dl with MCV 85 fL, reticulocytes 60000/*mm³*
- *PLT 20.000/mm³*
- WBC 1580/mm³
- **N 380/mm³**
- ***IgG 350 mg/dl, IgA 60 mg/dl, IgM 6 mg/dl***

CT scan: **fistulizing ileitis and diffuse lymphadenopathies (PET+)**.

September 2019

Lymph node biopsy: negative for lymphoproliferative syndromes

Started antibiotic therapy for ileitis and increased eltrombopag

2020	2021	2022	2023	2024	2025

Late 2019

Medullar hypocellularity and peripheral cytopenias

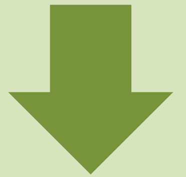
Aplastic anemia in previous ITP

Increased eltrombopag to 150 mg/day

Early 2020

Persistent hypogammaglobulinemia with frequent infections

Common Variable Immunodeficiency (CVID)



Started IVIG 30 gr every 15 days

Reassesement after 6 months

→ BOM: cellularity 80%, no marrow fibrosis

→ Fewer recurrent infections

→ **Fluctuating EBV DNA viral load**

CVID — Common Variable Immunodeficiency

1:25,000
Prevalence
Most common PID

<400
IgG (mg/dL)
diagnostic threshold

20–30y
Mean age
at diagnosis

8–12×
Relative risk
of lymphoma

🔎 Diagnostic Criteria (ESID)

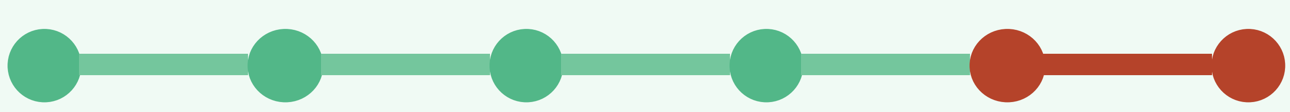
- Serum IgG < 2 SD for age (adults <400 mg/dL)
- At least IgA or IgM also reduced
- Absent/poor vaccine response
- Onset after 2nd year of life
- Other causes of hypogammaglobulinaemia excluded

🩺 Clinical Presentation

- Recurrent sinopulmonary infections (97%)
- Bronchiectasis on chest CT
- Chronic diarrhoea / malabsorption
- Lymphadenopathy / splenomegaly

Mean diagnostic delay: 5–7 years

⚙ Pathophysiology



Maturation block → mature B fails to differentiate into plasma cell → IgG/IgA/IgM ↓↓

Known genes: TACI, BAFF-R, ICOS, CD19, CD81 (single-gene defects <20% of cases)

⚠ Complications

Pulmonary:	Bronchiectasis, Granulomatous Lymphocytic Interstitial Lung Disease GLILD (30%)
GI:	Enteropathy, sprue-like, Giardia
Autoimmune:	ITP, AIHA, Evans syndrome (10–20%)
Oncologic:	Lymphoma (NHL/HL), gastric cancer

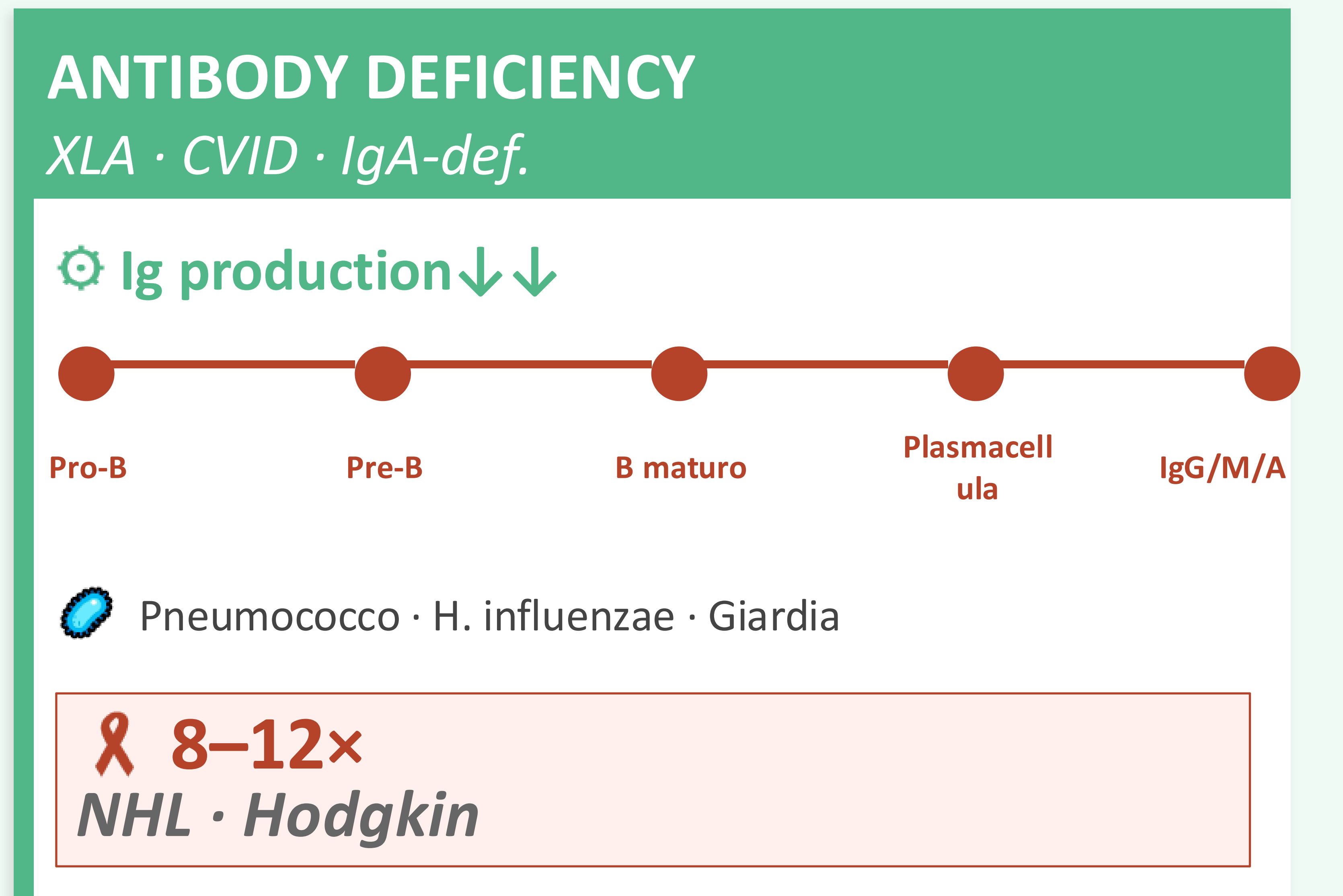
💊 Treatment

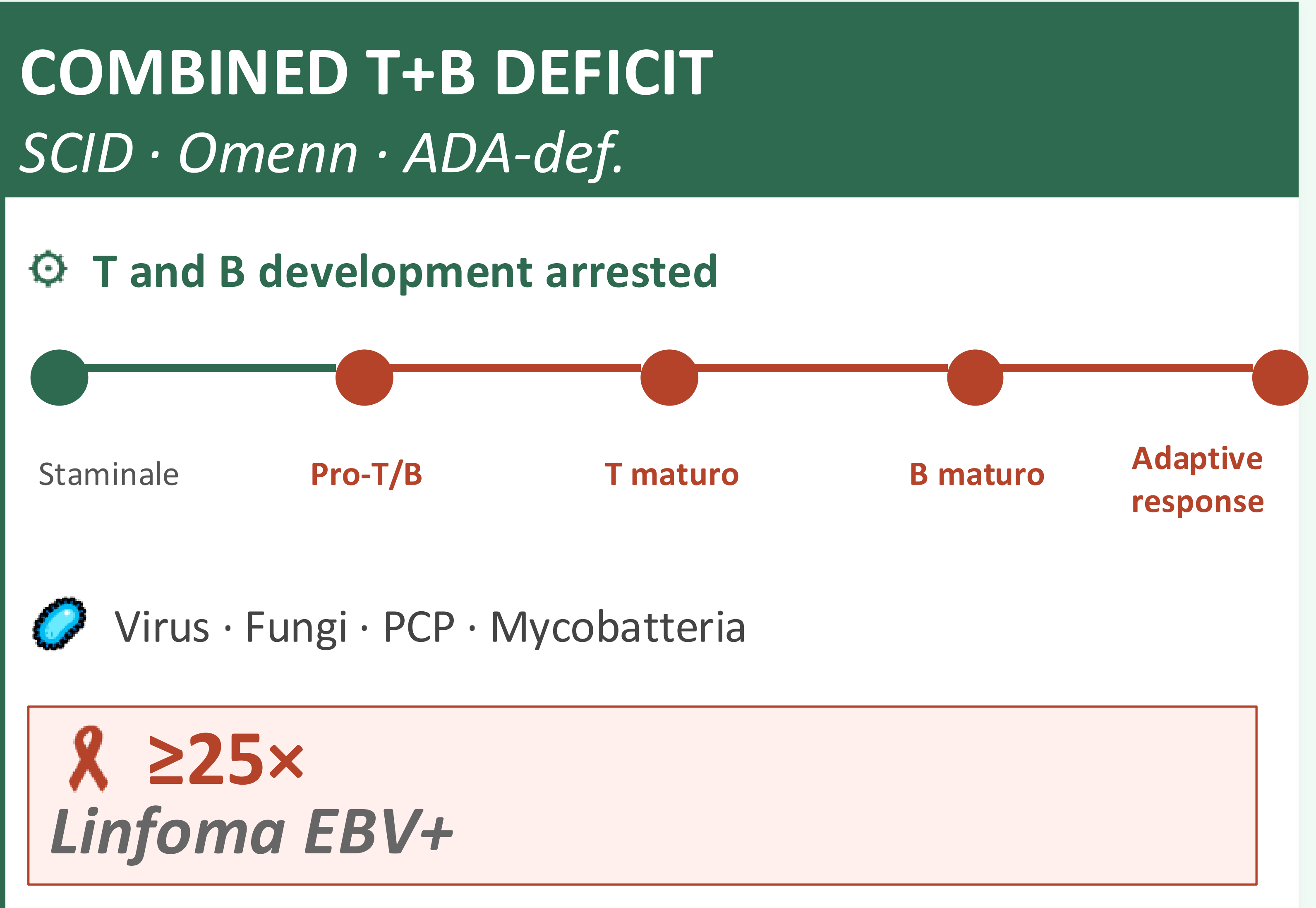
IVIg:	400–600 mg/kg every 3–4 weeks
SCIg:	Alternative: self-administration
Target:	Trough IgG levels >700 mg/dL
Infections:	Targeted antibiotics + prophylaxis
Lymphoma:	ABVD/R-CHOP + IVIg maintained

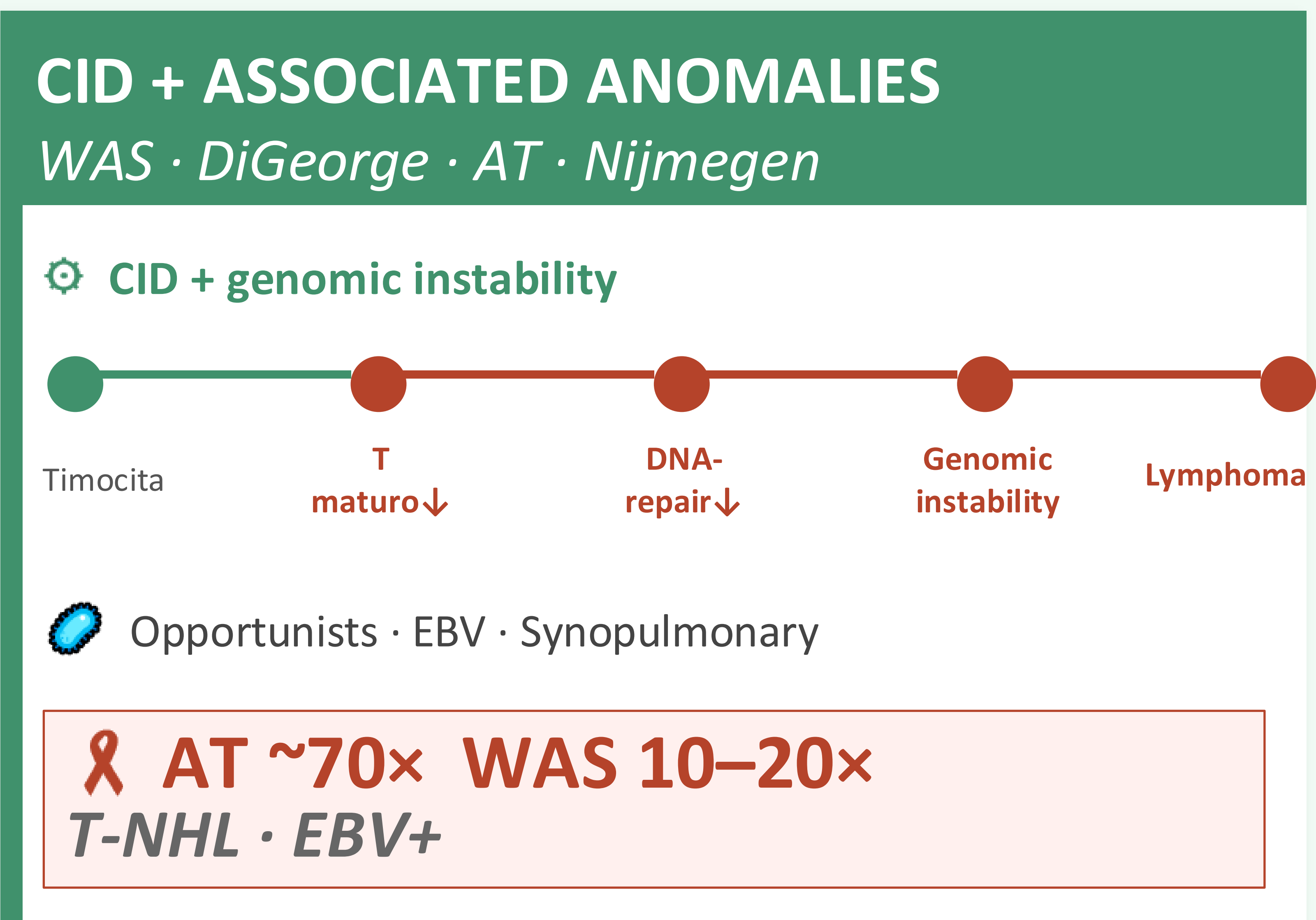
🎗 CVID & Lymphoma

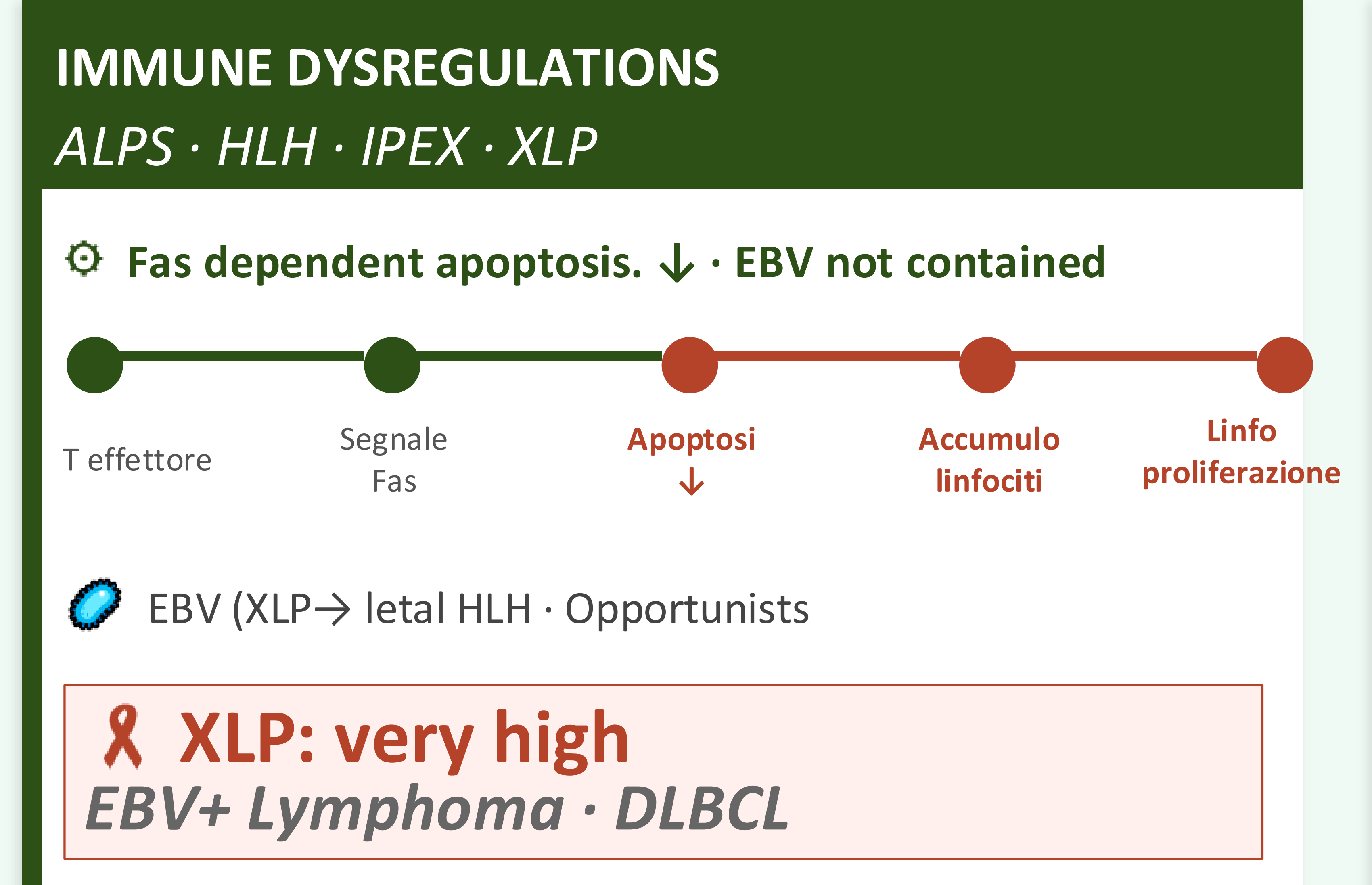
Type:	NHL (DLBCL), Hodgkin lymphoma
Risk:	8–12× vs general population
Mortality:	~30% of deaths in CVID patients
EBV:	EBV-LMP1+ in 30–40% of cases
Monitoring:	EBV-DNA + LDH every 6 months

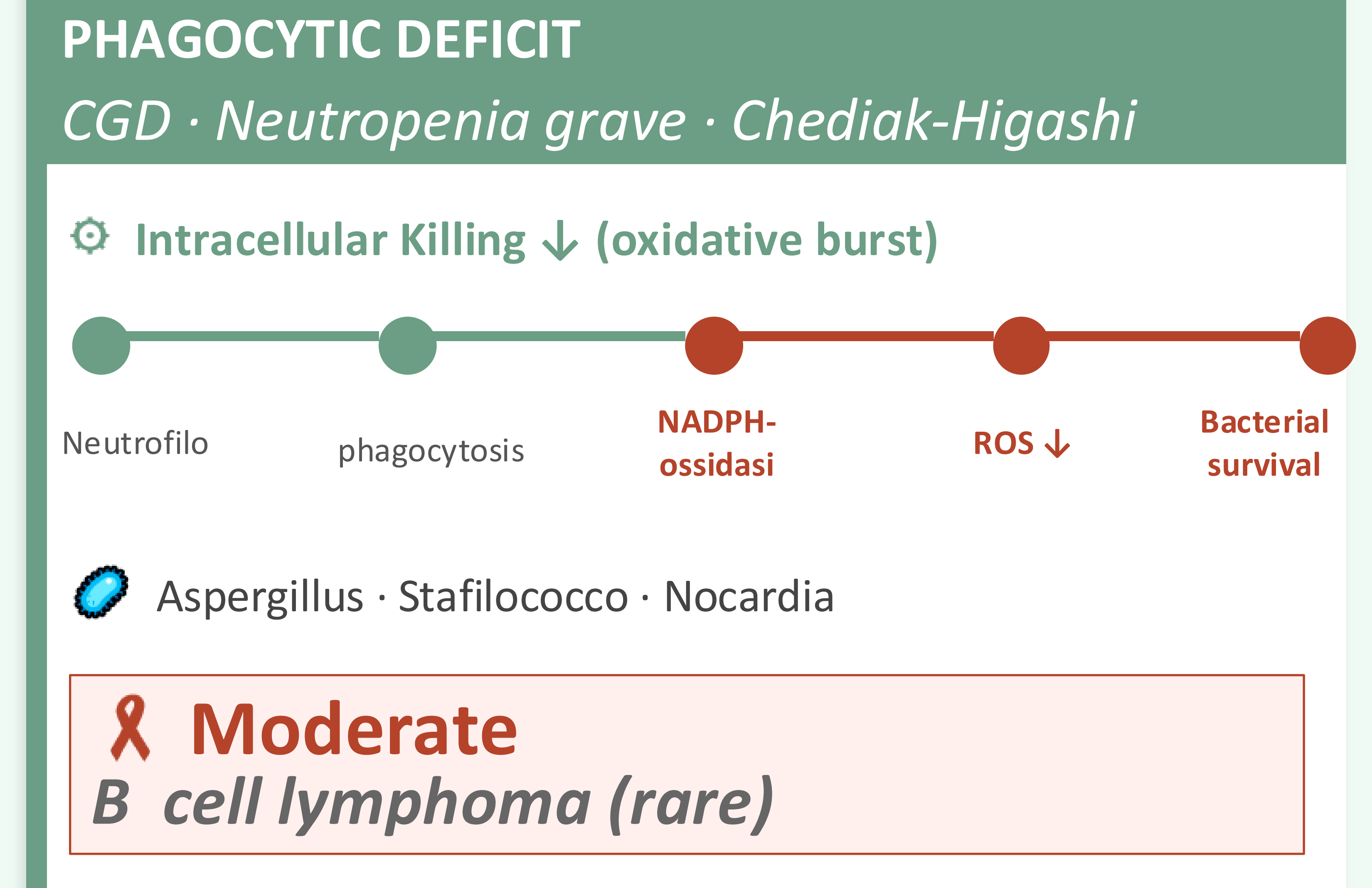
Pathogenic mechanism by category of PID

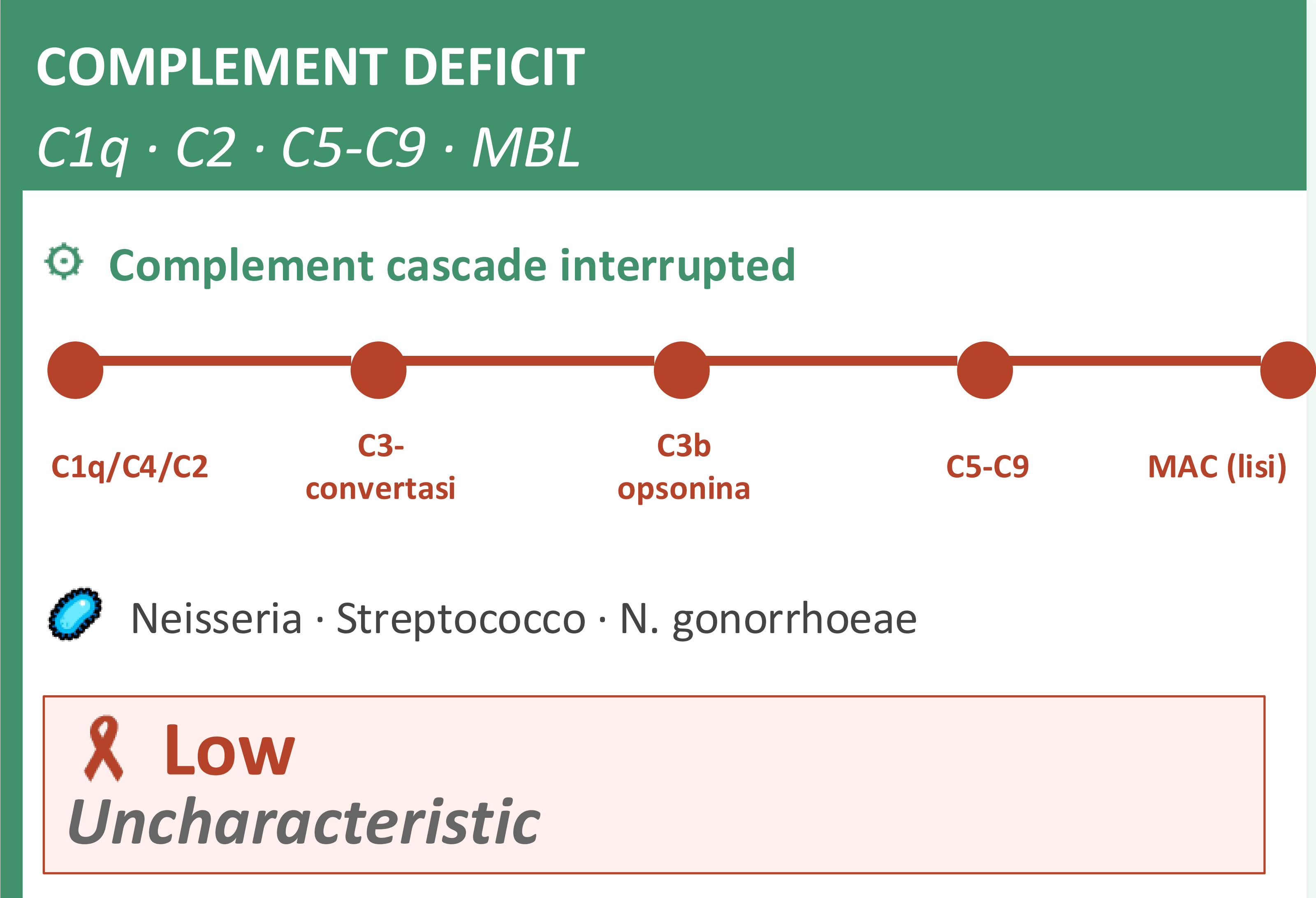












Pathophysiology of lymphomagenesis: key mechanisms

DEFECTIVE IMMUNE SURVEILLANCE

- Reduced NK/CTL cytotoxicity
- IFN-γ and perforin deficit
- Failure to eliminate transformed cells

CHRONIC EBV INFECTION

- Uncontrolled EBV → polyclonal B proliferation
- LMP1 activates NF-κB
- Prevalent in SCID, XLP, WAS

LYMPHOCYTE DISREGULATION

- Chronic hypo/hyperactivation of B cells (CVID)
- Autoreactive lymphocyte accumulation (ALPS)
- Fas-dependent apoptosis deficiency

GENOMIC INSTABILITY

- Deficit DNA-repair (AT, Nijmegen)
- Aberrant TCR/BCR rearrangement
- p53, c-MYC mutations

Fekrvand et al., J Clin Immunol 2024; Cheng et al., Clin Immunol 2024

2020	2021	2022	2023	2024	2025

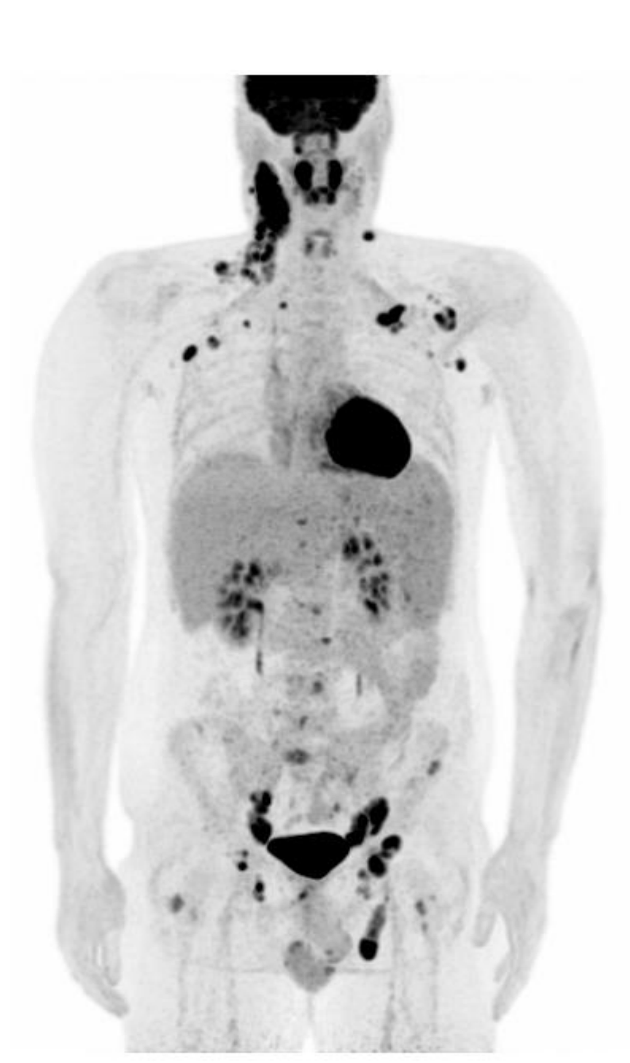
LTC lymphadenopathy and weight loss

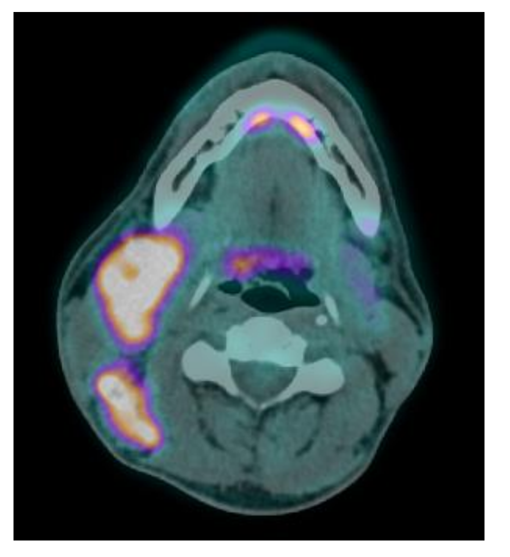
<u>FDG- PET scan:</u> supra- and infradiaphragmatic lymphadenopathy, SUV max in LTC lymphoadenopathy (16.7)

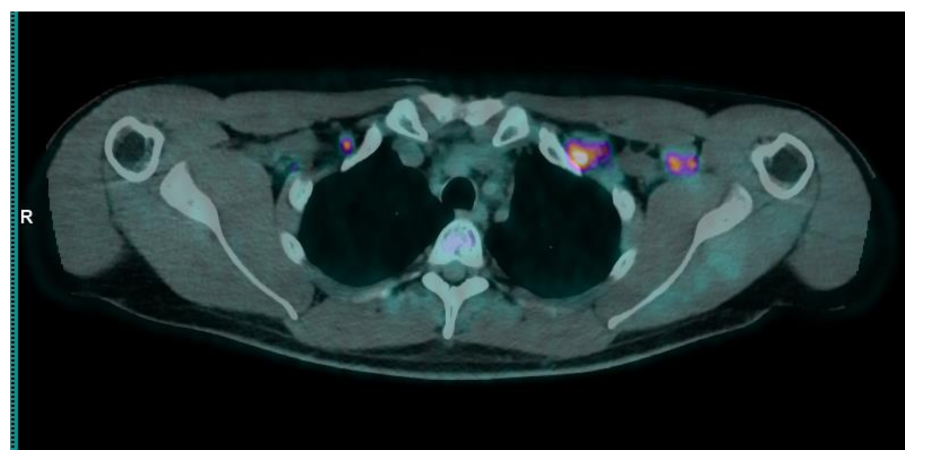
<u>CT scan:</u> multiple lymphadenopathies, hepato- and splenomegaly

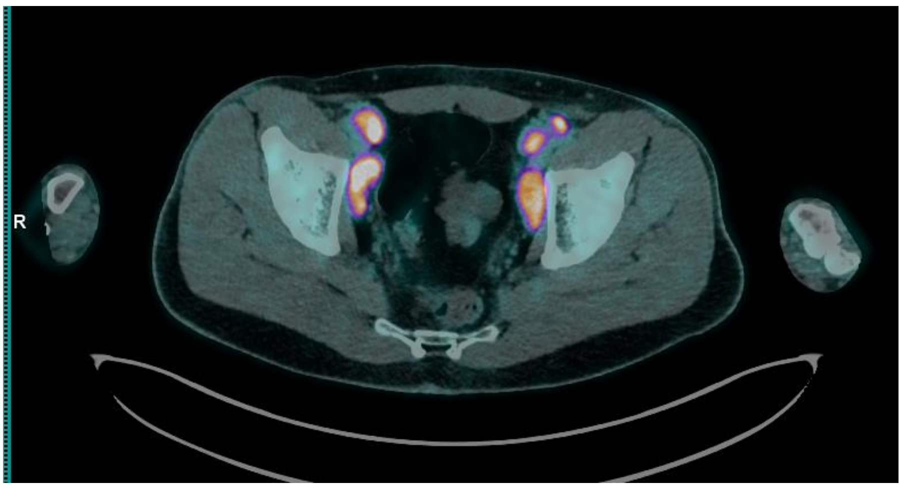
<u>BOM:</u> absence of lymphoid infiltration. Cellularity 50%

<u>Lymph node biopsy</u>: classical **Hodgkin lymphoma, mixed cellularity type**









baseline

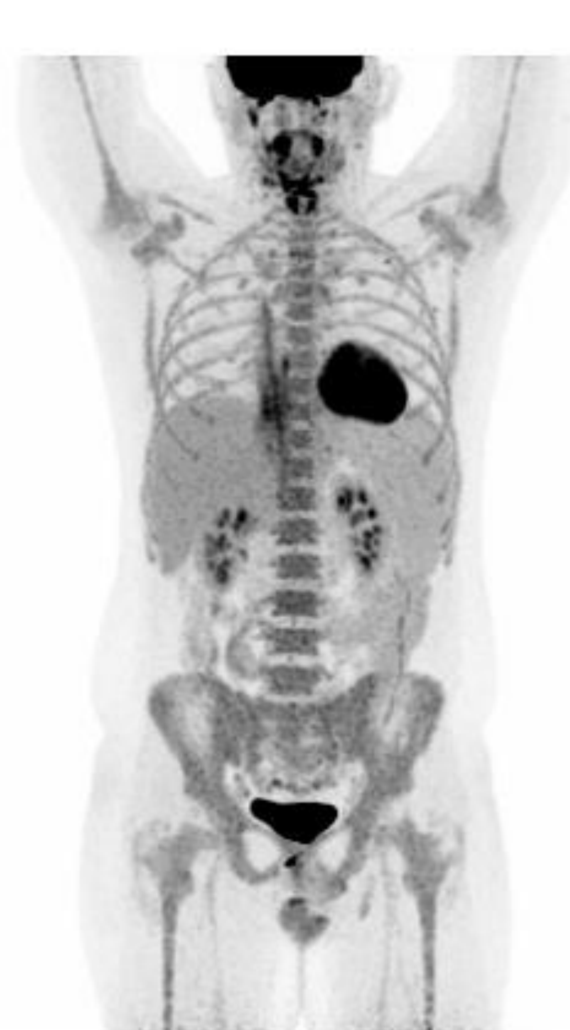
2020	2021	2022	2023	2024	2025

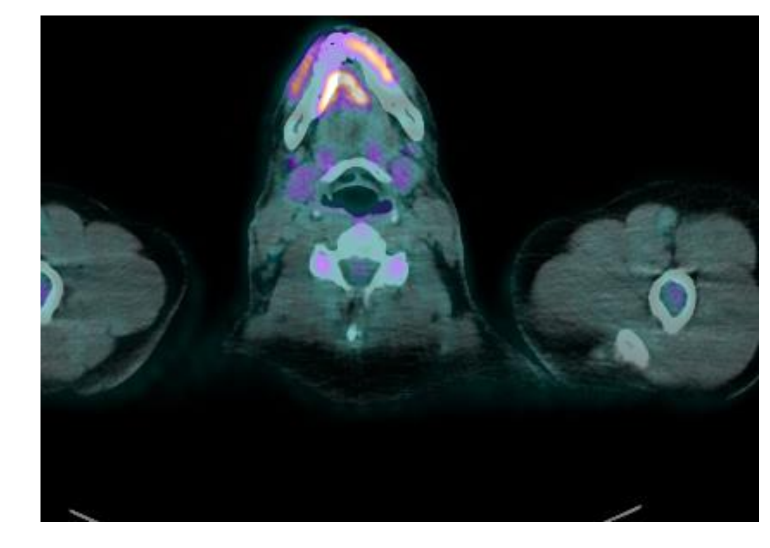
HL in CVID

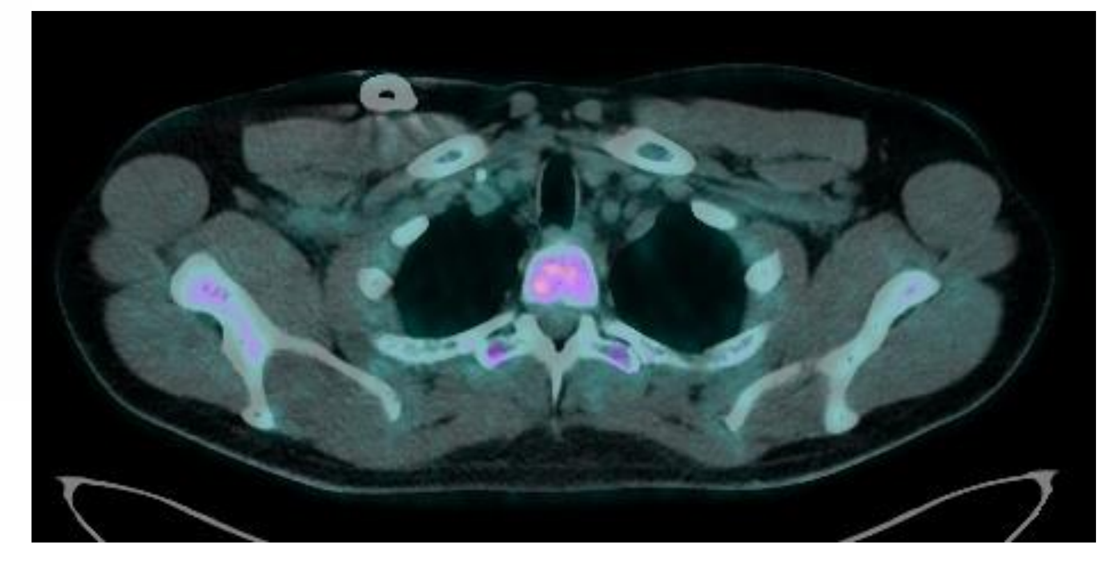
Medications:

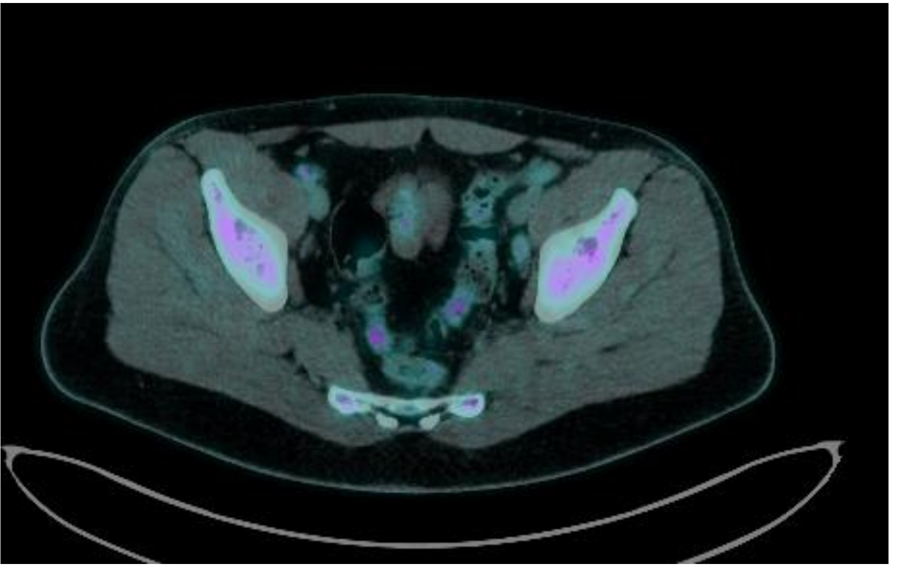
ABVD for 6 cycles
Interim PET → CR

Complications:
SARS-CoV2 infection and febrile neutropenia.







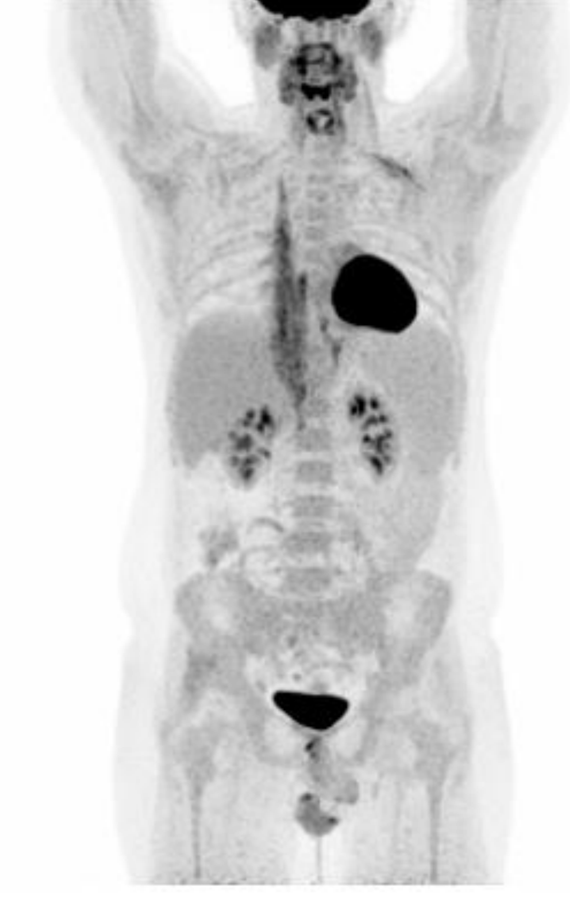


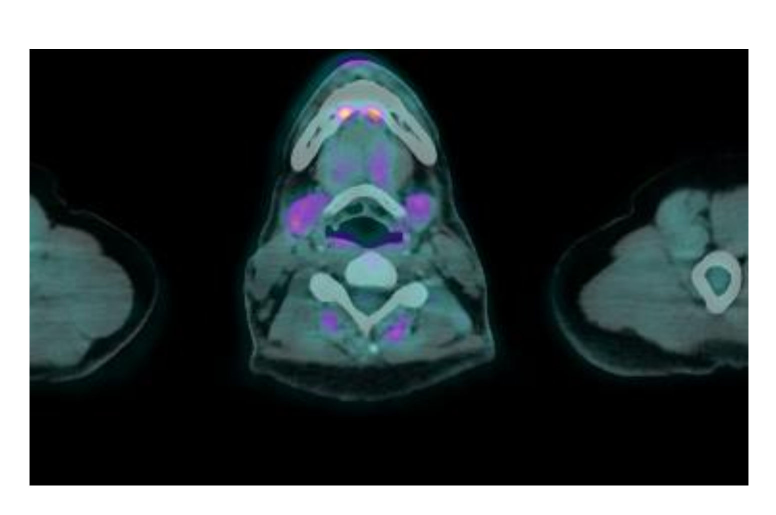
interim

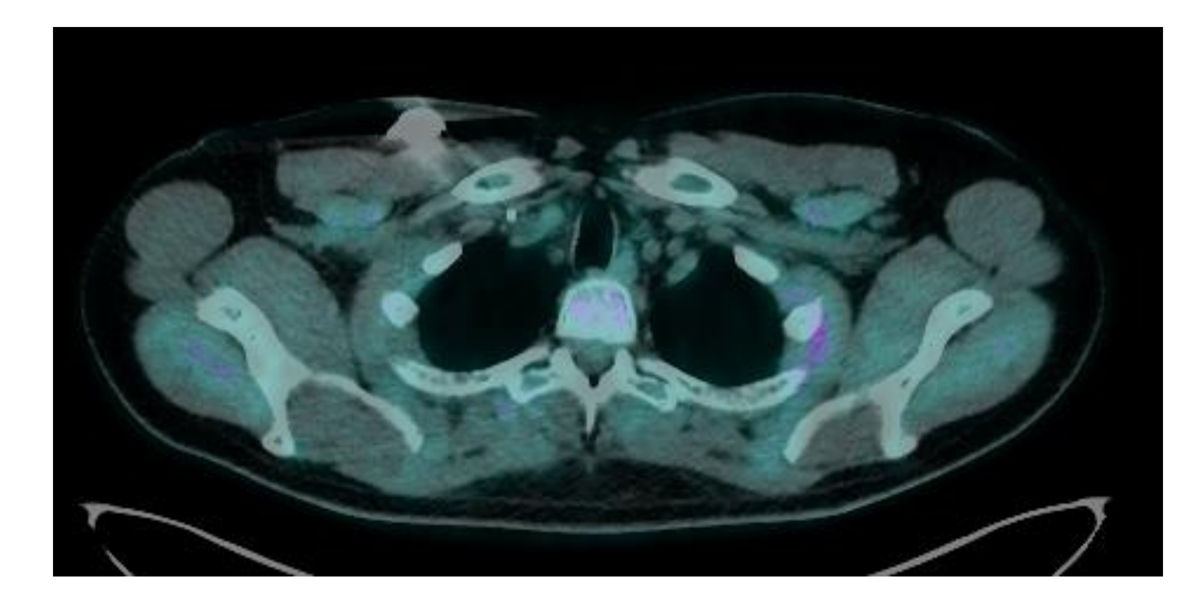
2020	2021	2022	2023	2024	2025

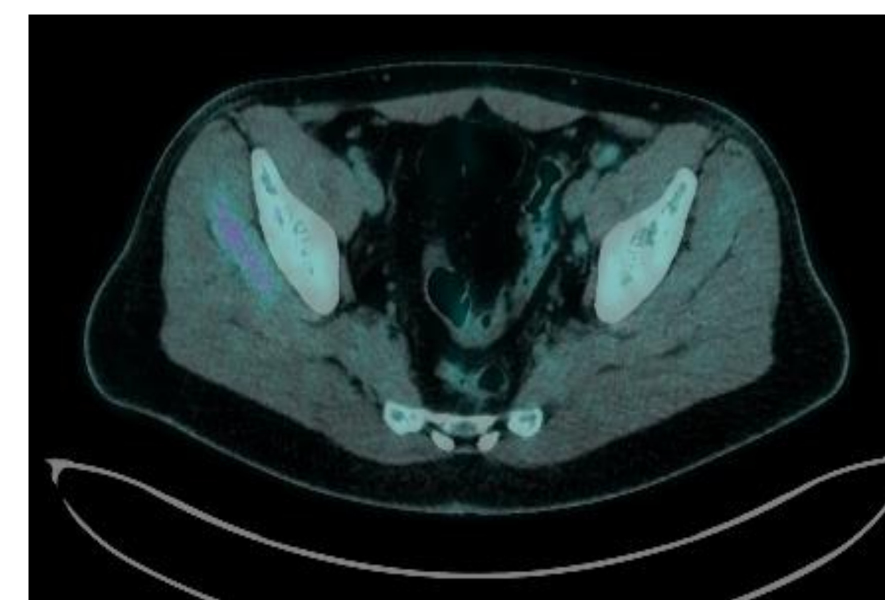
HL in CVID

End of Treatment: complete response at PET and CT scan









End Of Treatment

2020	2021	2022	2023	2024	2025

Early 2023

ITP relapse with PLTs 10.000/mm3
- New cycle of **IVIG** 0.4 gr/kg for 5 days
- Shift to **Romiplostim** 1 mcg/kg

Partial response

Middle 2023

He was admitted to hospital for severe fatigue and dyspnea during exertion.

Clinical evaluation:
- Slight jaudice

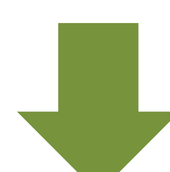
CBC:
- **Hb 7 gr/dl**
- MCV 110 fL
- PLT 490.000/mm3
- WBC 5860/mm3

2020	2021	2022	2023	2024	2025

Hemolytic markers:	
Bilirubin	2.02 mg/dL
LDH	350 U/L
Reticulocytes	275000 x 10^9/L
Haptoglobin consumption	
Other tests	EPO 100 U/L, viral serologies and quantiferon negative
DAT	Positive for IgG
BM evaluation	Not lymphoid infiltration
Contrast enhanced CT	Small LTC lymphoadenomegalies

Lymph node biopsy: negative for lymphoproliferative syndromes.

Diagnosis:
Autoimmune hemolytic anemia



EVANS SYNDROME
association of autoimmune hemolytic anemia (AIHA) and
immune thrombocytopenic purpura (ITP)

Treatment
Prednisone 1 mg/kg day → complete response.

Surveillance in CVID

⚠ Red Flags Clinics

- Persistent lymphoadenomegaly (>6 weeks)
- Progressive splenomegaly
- Fever without infectious causes
- Weight loss >10% in 6 months
- Increased LDH e β2-microglobulin
- EBV monoclonal proliferation (increasing DNA viral load)
- Unexplained cytopenias

Discussion key points

Evans syndrome can be a manifestation of lymphoma?

Yes: in CVID, ITP + AIHA can precede lymphoma by months. The lymphoma itself causes dysregulation of B autoantibodies. Lymphoma remission has resolved Evans syndrome

How to manage severe thrombocytopenia during ABVD?

- Pre-CT Rituximab to control ITP/AIHA + red cells transfusions for Hb < 8 g/dL
- ABVD not suspended: myelosuppression from lymphoma is the main cause of cytopenias

Ig: continue during chemotherapy?

Yes, absolutely. Maintain trough levels ≥ 800 mg/dL. During CT the risk of infection is amplified by neutropenia + hypogammaglobulinemia

HSCT as consolidation?

Allogenic HSCT potentially corrects CVID, eliminates Evans risk and consolidates lymphoma remission in a single step.

But is not yet a standardized procedure in these pathologies

HSCT in PID: when to transplant?

ABSOLUTE INDICATIONS

- **SCID (all forms)** urgent within 3.5 months, survival > 90%
- **Wiscott-Aldrich (WAS ≥ 3)** before lymphoma, hemorrhages, severe autoimmunity
- **CGD grave:** recurrent refractory infections or visceral granulomas
- **Chediak-Higashi:** only curative therapy in the accelerated phase (HLH)
- XLP (Purtilo): after HLH-EBV episode: prevents lethal recurrence

SELECTIVE INDICATIONS

- **CVID with lymphoma**, **GLILD or refractory cytopenia**
- **ALPS with lymphoma or refractory autoimmunity**
- **Deficit MHC class II** (bare lymphocyte syndrome)
- **AT**: severe immunological component only

KEY POINTS

- Before severe infections → each infection worsens the outcome
- SCID <2 yrs → survival > 90% vs 70% if late
- Preferred Matched Sibling Donor → but improved results with MUD
- Active lymphoma → remission first, then HSCT

GLILD: Granulomatous-Lymphocytic ILD · MSD: Matched Sibling Donor · MUD: Matched Unrelated Donor · RIC: Ridotta Intensità

Take Home Messages

1	CVID carries 8–12× elevated lymphoma risk; NHL/HL account for ~30% of deaths
2	EBV plays a central role in CVID associated-lymphomagenesis. Monitor EBV-DNA regularly
3	Evans syndrome must prompt immediate lymphoma work-up
4	Standard CT is feasible – IVIg must be continued
5	Allogenic HSCT can address both CVID and Lymphoma
6	Lifelong structured surveillance is mandatory: any rise in EBV viral load should prompt early intervention

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Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

S.C. Ematologia
Gruppo Linfomi
Gruppo Citopenie Immuni

Thanks for your attention!

S.C. Medicina Interna
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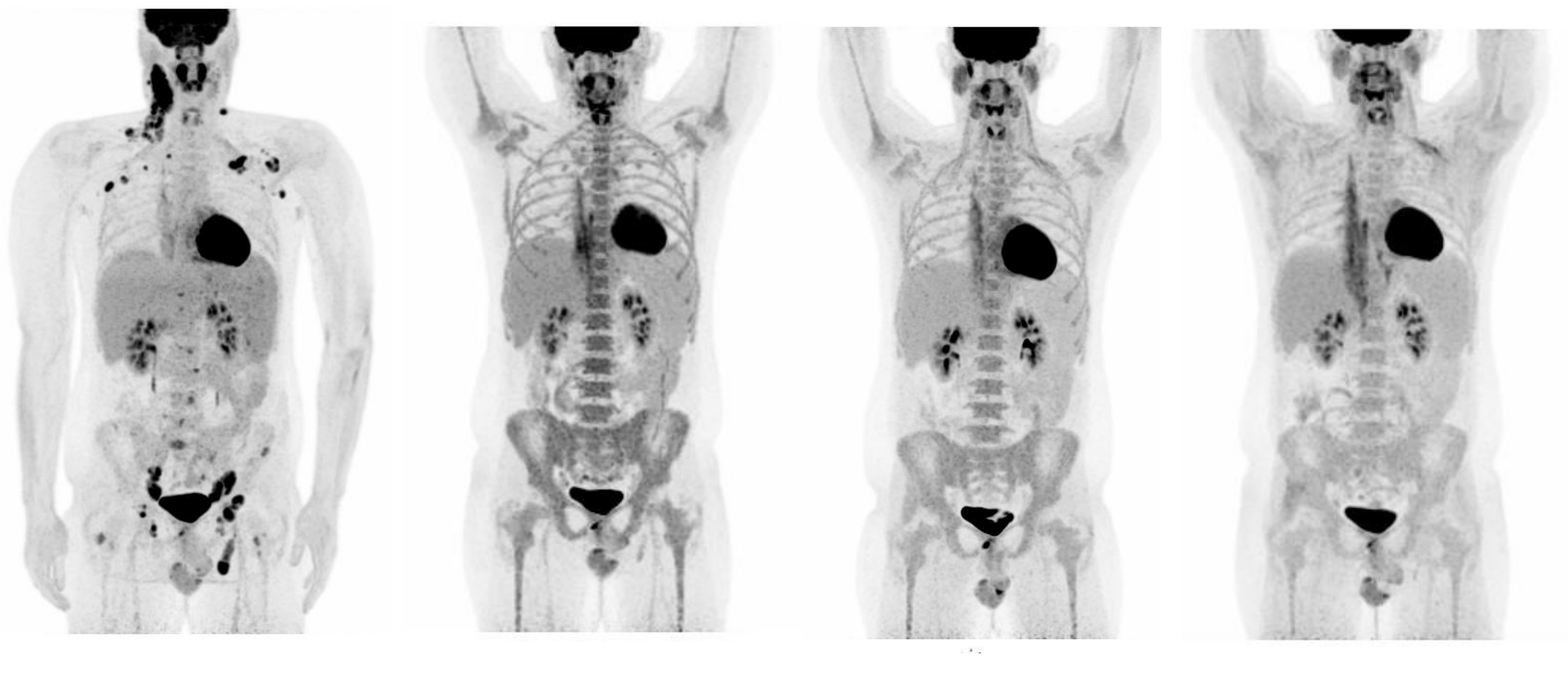
IPINET per le immunodeficienze primitive
dell'adulto e sdimndromi autoinfiammatorie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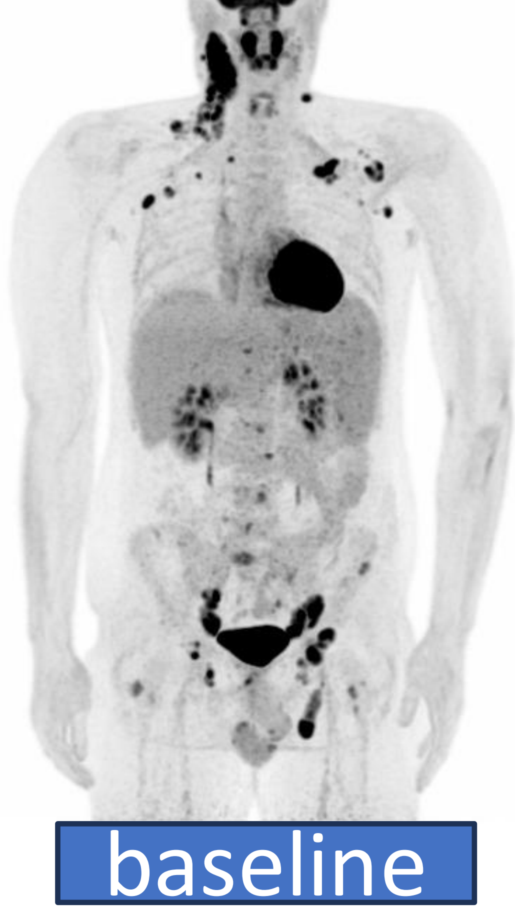

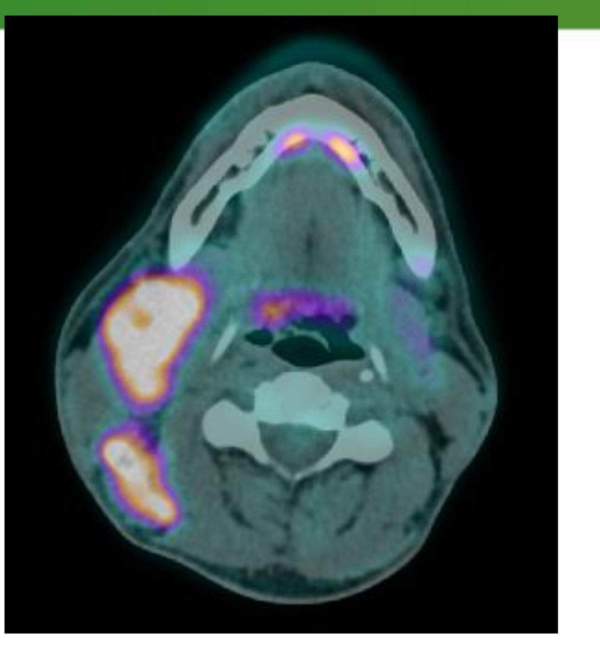

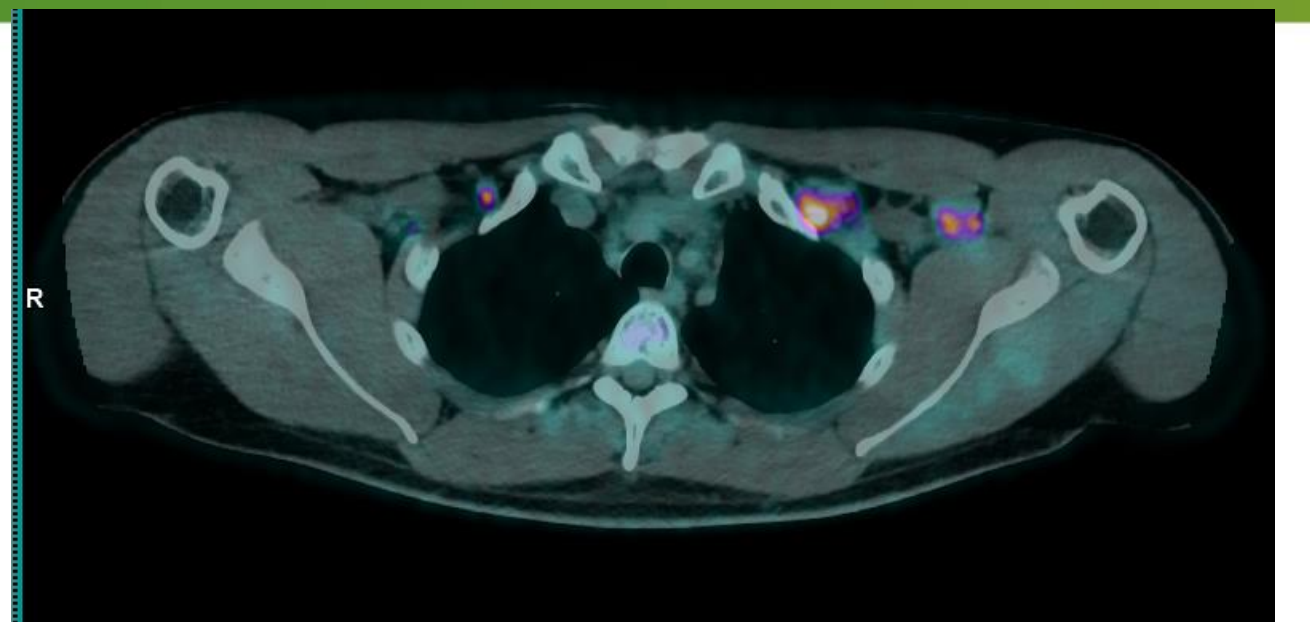

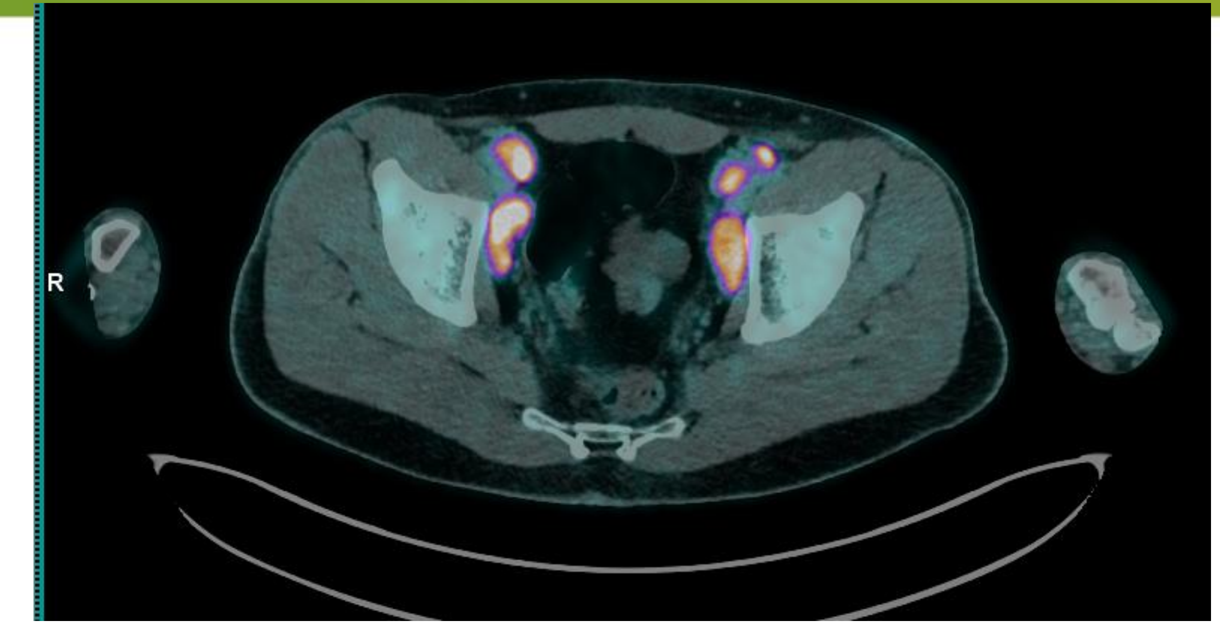

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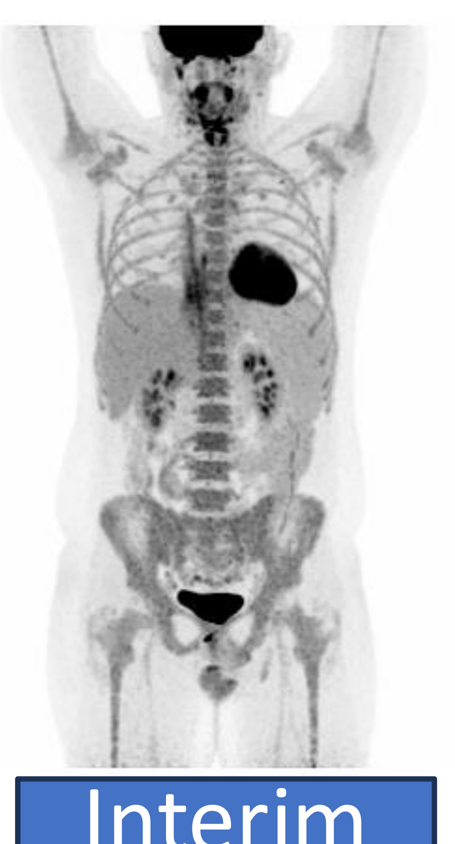

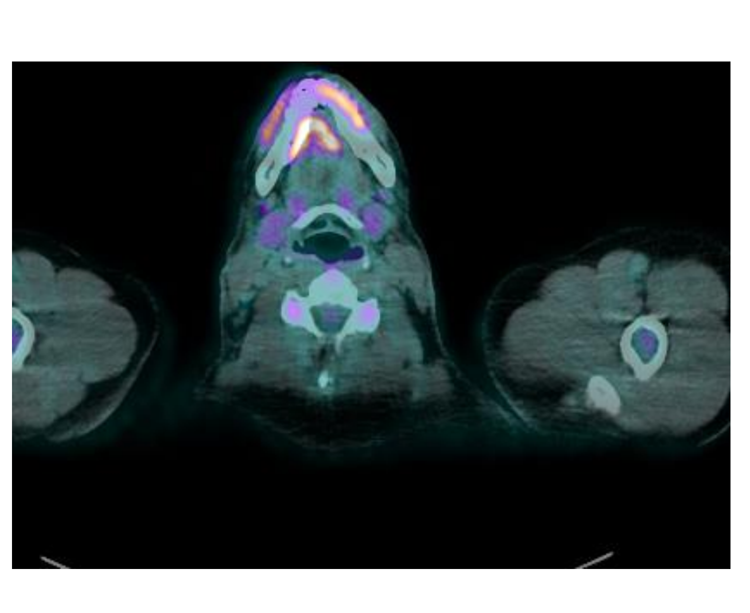

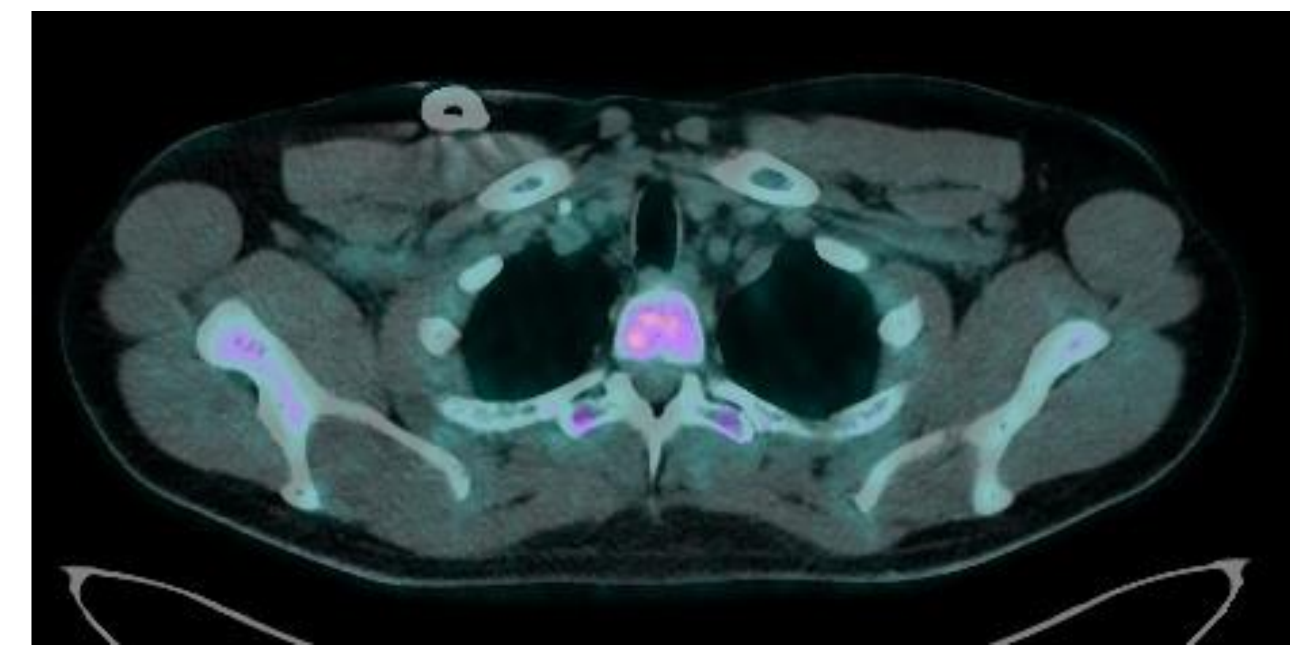

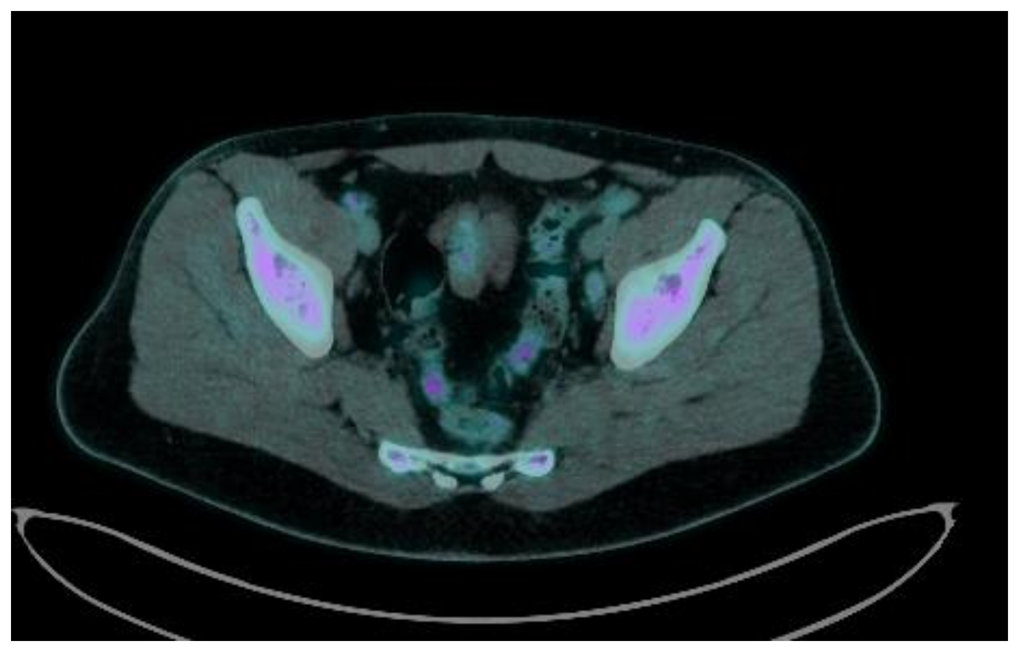

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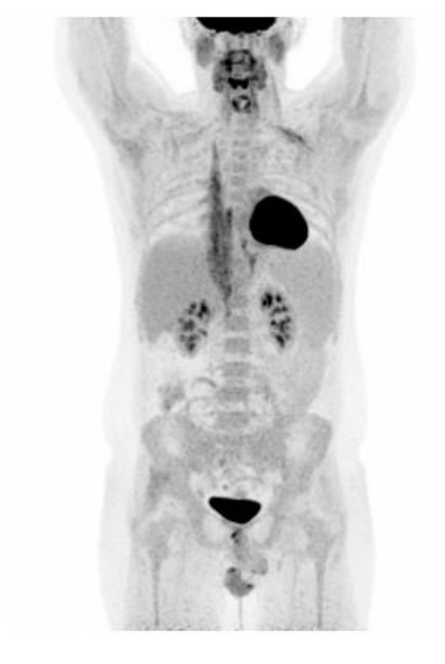

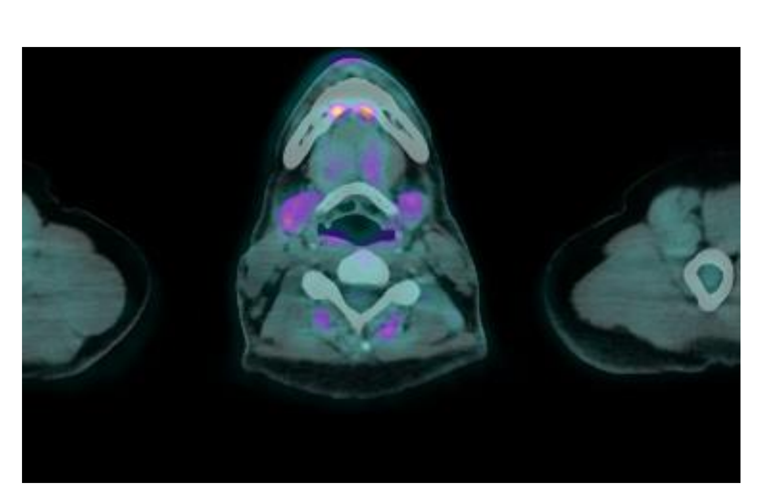

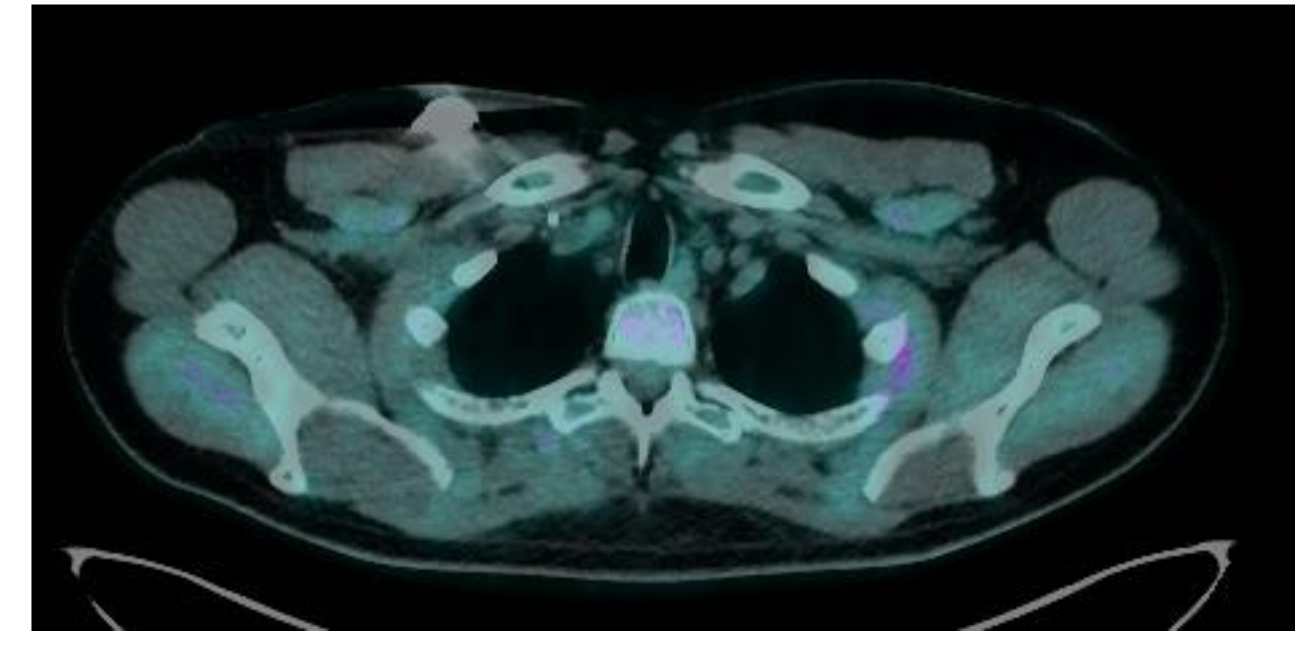

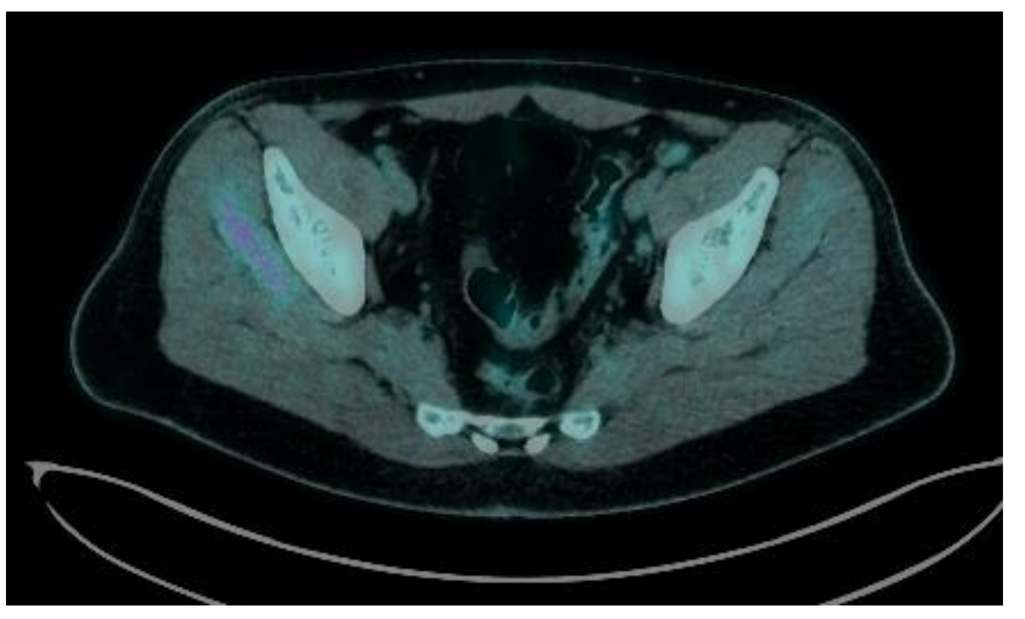

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