Interesting Case

(Post-transplant lymphoproliferative disorder)

An 11-year-old girl with fever and abdominal pain

28 มิถุนายน 2556

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เด็กหญิง อายุ 11 ปี ภูมิลำเนา อ. สามเงา จ. ตาก

CC: มีไข้ และ ปวดท้องมา 3 วัน

PI: 3 วันก่อนมารพ. ผู้ป่วยมีไข้สูงทั้งวัน ไม่ไอ ไม่มีน้ำมูก ไม่อาเจียน ถ่ายอุจจาระปกติ มารดาให้กินยาลดไข้ แต่อาการไม่ดีขึ้น มีไข้ตลอด วันต่อมาเริ่มอ่อนเพลีย กินได้ลดลง บ่นปวดท้องด้านซ้ายบนเป็นพักๆ ไม่อาเจียน ยังมีไข้ตลอด มารดาจึงพามารพ. หลังจากรับไว้ในรพ. ผู้ป่วยมีไข้ตลอด ปวดท้องด้านซ้ายบนและกลางท้องแบบบีบๆ เป็นพักๆ ไม่สัมพันธ์กับอาหาร กินได้ลดลง ไม่อาเจียน ถ่ายอุจจาระเละๆ ไม่มีมูกเลือดวันละ 3-4 ครั้ง

PH: - เป็นบุตรคนเดียว แรกเกิดปกติ ได้รับ vaccine ครบตามกำหนด

- Underlying end stage renal disease (จาก focal segmental glomerulosclerosis) ตั้งแต่อายุ 7 ปี ได้รับการผ่าตัด kidney transplantation (ไตมารดา) เมื่อ 23/7/55 หลังจากเปลี่ยนไตได้รับ prednisolone, prograf (tacrolimus, FK-506) และ myfortic (mycophenolate, MMF)
- 30/11/55 นอนรพ. ด้วยเรื่องไข้ ได้รับการวินิจฉัยว่าเป็น CMV infection จากการที่ตรวจพบ CMV viral load 159,783 copies/mL ได้รับการรักษาด้วย ganciclovir 2 สัปดาห์และตามด้วย valganciclovir
- Current medications : prograf, myfortic, prednisolone, amlodipine, apresoline, lipitor, valganciclovir, insulin, cotrimoxazole

Physical examination:

GA : An active girl, BW 41.8 kg (P50-75), height 131 cm (P10)

Vital signs: BT 39.1° C, PR 120/min, RR 24/min, BP 92/60 mmHg

HEENT : mild pale conjunctivae, no icteric sclera, lymph node – not palpable

mild injected pharynx, no tonsillar enlargement

Heart and lungs : normal

Abdomen : no distension, active bowel sound, soft, mild tender at LUQ and peri-umbilical area,

no guarding, no rebound tenderness, no hepatosplenomegaly

Extremities : no edema

Investigations:

CBC : Hb 11.3 g/dL, Hct 34.4%, WBC 2,270/cu mm (N 85, L 7, M 3, B 3, E 2%),

platelets 320,000/cu mm

Urine : Sp.gr. 1.006, pH 7, protein & sugar – negative, no WBC, no RBC

BUN/Cr 10/0.9 mg/dL; Na 136, K 4.3, Cl 107, CO_2 20 mmol/L

LFT : Total protein 5.9 g/dL (albumin / globulin 3.3 / 2.6 g/dL), ALP 79,

AST 30 U/L ALT 20 U/L; TB / DB 0.71 / 0.07, cholesterol 123 mg/dL

Prograf level : 7 ng/mL

Problem list:

- Acute febrile illness with acute colicky abdominal pain and diarrhea
- Focal segmental glomerulosclerosis (post renal transplantation)

Differential diagnosis:

- Infections (enteritis or colitis) from bacterial infections : salmonella, shigella, E. coli
- Opportunistic infections : TB, MAC, CMV, EBV
- Typhlitis
- Inflammatory bowel diseases
- Post-transplant complications
- Post-transplant lymphoproliferative disorder (PTLD)
- Mycophenolate-associated colitis

Further investigations:

Stool exam : no gross blood, no mucous, no WBC, no RBC

Stool occult blood : negative

Stool culture : pending

Serum amylase 32 U/L, serum lipase 8 U/L

CXR : normal

Work up for tuberculosis:

TT : negative (3-mm induration at 72 hours)

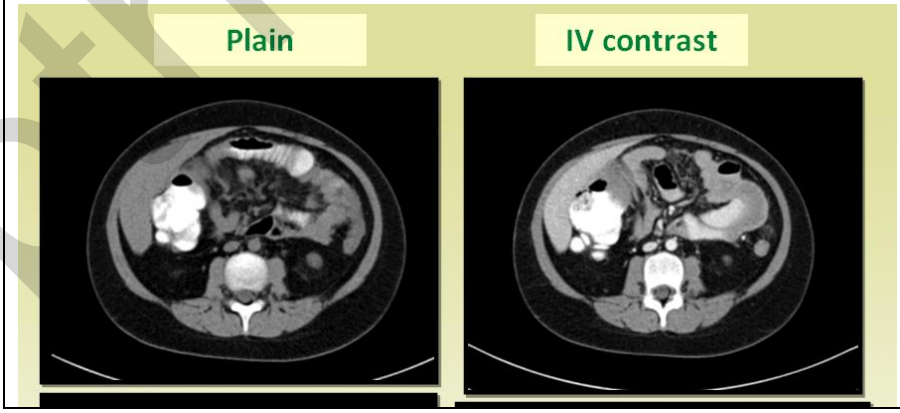
Sputum AFB : negative x 3 days Sputum C/S for TB : contaminate

Stool AFB : negative Stool culture for TB : contaminate

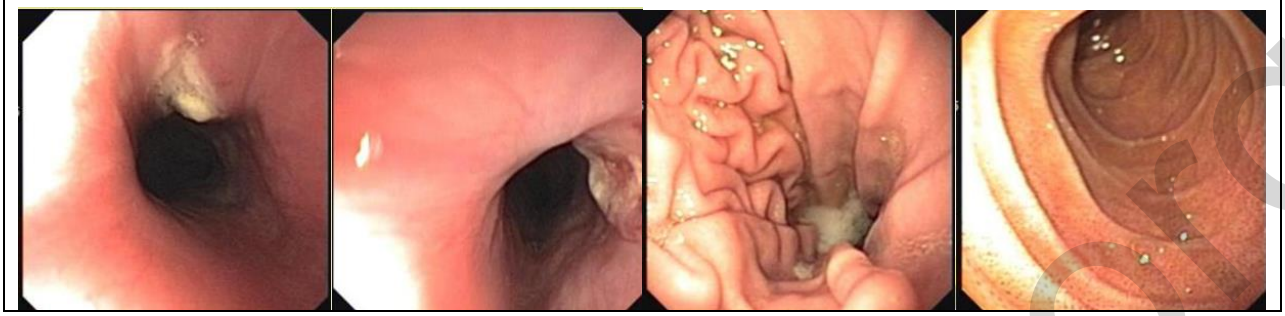
Viral load and serology

Date	Before treatment	3/12/55	17/12/55	7/2/56
EBV IgG/M	NA	-/-		-/-
EBV viral load (copies/mL)	NA	<1,000		11,500
CMV IgG/M	-/-	-/-		NA
CMV viral load (copies/mL)	NA	159,783	25,480	5,060

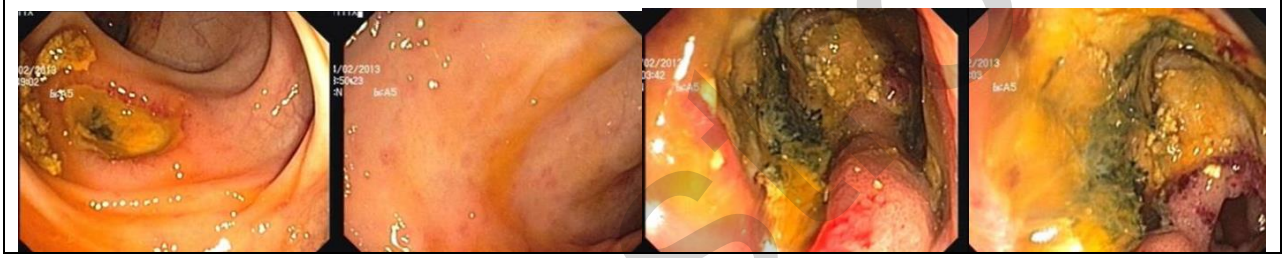
CT abdomen: Focal irregular wall thickening involving cecum and IC valve, associated with adjacent lymph node enlargement. Mild hepatomegaly, normal pancreas and kidneys.



Esophago-gastro-duodenoscopy: 1 deep ulcer at mid-esophagus, others- normal.

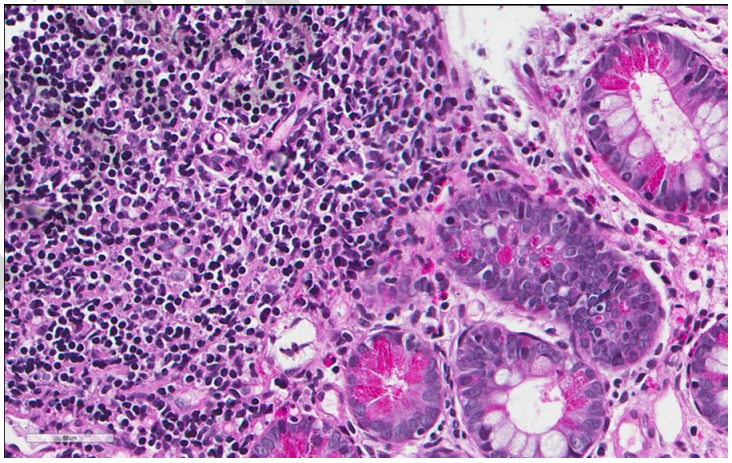


Colonoscopy: 1 large, deep ulcer at rectum **and** deformed IC valve with large ulcer and necrotic tissues

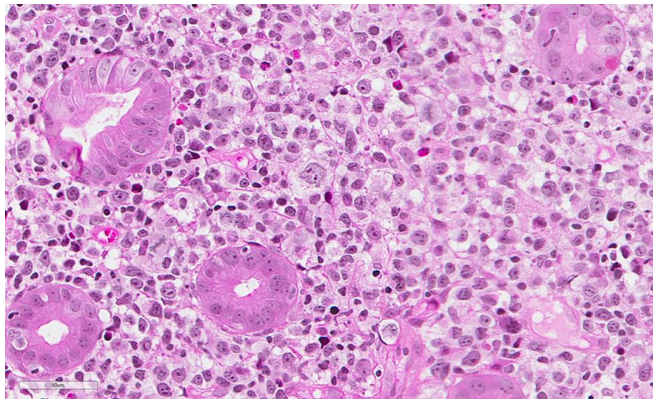


Pathology:

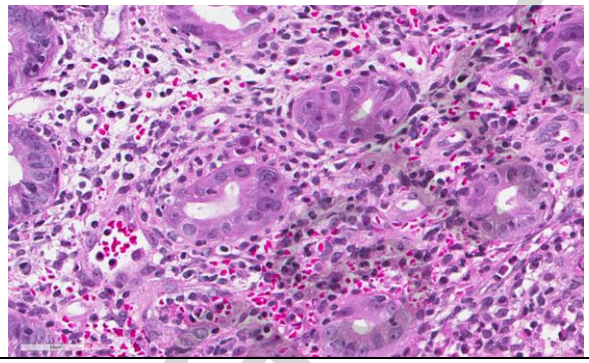
Terminal ileum (40X) : Numerous reactive lymphocytes (chronic inflammation)



IC valve (40X) : Abnormal round cells (pink cytoplasm, large nucleus with nucleoli) infiltrate in lamina propria, positive for CD20 staining. These cells could be non-Hodgkin lymphoma.



- **Rectum : inclusion body**



Diagnosis:

- Post-transplant lymphoproliferative disorder (PTLD) [diffuse large B cell lymphoma]
- CMV colitis

Treatment: PTLD : staging, discontinue prograf and MMF, start everolimus and continue prednisolone
CMV colitis : Ganciclovir (10 mg/kg/day)

Progression:

- Esophageal ulcer improved after ganciclovir.
- After discontinuation of prograf, there was no improvement of IC valve lesion.

After 2 courses of rituximab, there was a slight improvement of IC valve lesion.

Hematologist suggestion: start CHOP/R (vincristine, doxorubicin, cyclophosphamide, prednisolone, rituximab) and the lesion improved after using this regimen.

Post-transplant lymphoproliferative disorders (PTLD)

- PTLD is an important complication of pediatric organ transplantation that represents a morphologic, immunophenotypic, and genotypic spectrum of disease.
- **Incidence** :
  - depending on type of organ graft and immunosuppressions
  - 1-4% in renal and liver transplantations
  - 20% in thoracic organ and intestinal transplantations
- Primarily EBV-mediated uncontrolled B-cell proliferation that occurs with decreased T-cell immune surveillance as a result of immunosuppression for graft survival.

Risk factors for PTLD in solid organ transplant

- **Early PTLD** (within 12 months after transplantation)
  - EBV infection : mismatch of EBV status (D+/R-), primary EBV infection and reactivation
  - Other viruses : CMV mismatch or CMV disease, human T-cell leukemia virus, HHV8, HCV, simian virus 40
  - Young recipient age (< 10-year-old)
  - Type of organ transplanted : kidney < liver < heart < heart/lung < lung < small bowel < multi-visceral
  - Immunosuppression : drugs (CNI, OKT3, ATG), intensity of immunosuppression and cumulative dose
- **Late PTLD**
  - Duration of immunosuppression
  - Type of organ transplantation
  - Older recipient (> 60-year-old)

Clinical assessments

- Clinical information includes:
  - EBV serostatus of transplant recipient and donor
  - CMV donor/recipient serostatus
  - Time from transplantation to PTLD diagnosis
  - Type of allograft
- An adequate physical examination is required but may be nonspecific.

Clinical manifestations

- **Symptoms/complaints**
  - Swollen lymph glands
  - Weight loss, fever or night sweat
  - Sore throat, chronic sinus congestion and discomfort
  - GI : anorexia, nausea and vomiting, abdominal pain, gastrointestinal bleeding, symptoms of bowel perforation
  - Others : cough and shortness of breath, headache, focal neurologic deficits
- **Signs**
  - Lymphadenopathy, tonsillar enlargement and inflammation
  - Hepatosplenomegaly
  - Subcutaneous nodules
  - Mass lesions

Investigations:

- **Blood tests**
  - CBC, LFT and renal function tests
  - EBV detection
    - EBV serology: anti-viral capsid antigen, anti-early antigen, anti-Epstein Barr nuclear antigen
    - EBV latent antigens : EBNA-1, EBNA-2, LMP-1

- EBV Viral load
  - CMV detection : pp65 antigenemia assay, CMV viral load
- **Radiographic imaging :** total body CT scan (head to pelvis)
- **Histopathology (gold standard for PTLD diagnosis) :** cell phenotype and lineage, clonality, presence of EBV (EBER in situ hybridization), expression of CD20, cytotoxic T-cell epitopes
- **Other tests:** usually for lymphoma work-up (bone scan, BM biopsy, CSF cytology)

World Health Organization (WHO) Classification (2008)

- Early lesions : plasmacytic hyperplasia, infectious mononucleosis-like lesion
- Polymorphic PTLD (polyclonal, monoclonal)
- Monomorphic PTLD (classify according to lymphoma they resemble)
  - B-cell neoplasms : diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, plasma cell myeloma, plasmacytoma-like lesion and other
  - T-cell neoplasms : peripheral T-cell lymphoma (not otherwise specified), hepatosplenic T-cell lymphoma and other
- Classical Hodgkin lymphoma-type PTLD

Prevention of PTLD

- Identify patient at high-risk for PTLD prior to transplantation + EBV serostatus
- American Society of Transplantation recommends that all seronegative recipients and all children < 1 year of age should be screened monthly for EBV viral load in the first year following transplantation.
- Antiviral prophylaxis
  - Chemoprophylaxis: Ganciclovir (limited data, may be useful in EBV D+/R-)
  - Immunoprophylaxis (EBV-neutralizing antibodies via IVIG) : uncleared data
- Preemptive management
  - Reduction of immunosuppression and giving antiviral agents
  - Insufficient evidence to dictate a specific course of action

Treatment of PTLD

- **Reduction or cessation of immunosuppression**
  - Primary treatment
  - Reduce dose to achieve 25–50% of the normal therapeutic whole blood trough level
  - Regression of PTLD lesions in up to 50% of cases
  - Expected clinical response within 2–4 weeks
- **Surgical resection / local irradiation**
  - Adjunctive therapy along with reduction of immunosuppression
  - Surgery for local complications: GI hemorrhage or perforation
  - Local radiotherapy : CNS lesions
- **Antiviral agents (acyclovir, ganciclovir) / passive antibody (IVIG)**
  - No evidence to support the use of antiviral agents in the absence of other interventions.
- **Monoclonal B-cell antibody therapy (anti-CD20) (rituximab)**
  - As the next step in PTLD treatment after reduction of immunosuppression
  - Response rate 70-100% and complete remission 30-70% (using rituximab alone)
  - Higher rate of relapse
  - Potential adverse events : tumor lysis-like syndrome, prolonged depletion of B cells, intestinal perforation at the PTLD site
- **Cytotoxic chemotherapy**
  - When the reduction in immunosuppression fails to control the disease
  - CHOP regimen (cyclophosphamide, adriamycin, vincristine, prednisolone)
  - Remission rates as high as 69% among patients with B-cell tumors
  - Intestinal involvement with necrosis and perforation at diagnosis may have predictive value for an aggressive course of early chemotherapy, even in early and EBV-associated PTLD.
- **Other treatment modalities**
  - Adoptive immunotherapy (cloned EBV-specific cytotoxic T cells)
  - Immunomodulatory / anti-cytokine therapy: alpha-interferon

Factors associated with poorer outcomes from PTLD

- Poor performance status
- Multisite disease
- Central nervous system disease
- T- or NK-cell PTLD
- EBV-negative PTLD
- Recipient origin disease relative to donor origin
- Co-infection with hepatitis B or C
- Monoclonal disease
- Presence of mutation of proto-oncogenes or tumor suppressor genes

References

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2. Végso G, Hajdu M, Sebestyén A. Lymphoproliferative disorders after solid organ transplantation: classification, incidence, risk factors, early detection and treatment options. Pathol Oncol Res 2011; 17: 443-54.
3. Mourad WA, Tulabah A, Al Sayed A, et al. The impact of the World Health Organization classification and clonality assessment of post-transplant lymphoproliferative disorders on disease management. Arch Pathol Lab Med 2006; 130: 1649–53.