Immunology

Cases Studies
in
Autoimmunity and Infectious Disease

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Case 1

- Patient Presentation
  - 22 y.o. male
  - Fever and sore throat
  - Enlarged, tender lymph nodes in neck for 24 hours
  - Very ill
  - Symptoms worsening

History

- Healthy preceding presentation
- No known recent contact with anyone ill
- Recent travel history
  - Southern African game farm
  - Malaria prophylaxis taken
  - Reported tick and mosquito bites

Past medical history

- Non-Hodgkin's lymphoma at age 11
  - Remained in remission
- No previous surgeries
- No significant family history
- No allergies
- No medications

Social history

- No smoking
- No illegal substance use
- No alcohol

Differential diagnosis

Rickettsia	CMV
Measles	HSV
Viral hepatitis	Rift Valley Fever
Malaria	Typhoid
EBV	Crimean Congo haemorrhagic fever

Physical examination

- Appeared ill
- Awake, alert, cooperative
- Not encephalopathic

Vitals

- Temperature: 38.5C (101.3F)
- Blood pressure: 124/76
- Heart rate: 100
- Respiratory rate: 16

General

- 3+ jaundice
- 2+ lymphadenopathy (soft & tender)
- Slight periorbital edema
- No neck stiffness
- Vision and hearing intact
- Pupils equal and reactive to light

ENT

- Nonexudative red inflamed throat
- Enlarged tonsils
- Chest clear

Examination

- Mild tenderness over liver and spleen
- Hepatosplenomegaly
- No seizures reported
- Normal reflexes
- No gait problems
- Faint, generalized rash

Admitted to isolation unit

Test	Result	Interpretation
Na	132 mEq/L	↓
K	4.6 mEq/L	
Cl	94 mEq/L	↓
CO2	22 mEq/L	
Urea	9.4 mmol/L	↑
Creatinine	1.52 mg/dL	↑
Bilirubin	12.7 mg/dL	↑
Bili (conjugated)	8.1 mg/dL	↑
ALP	383 U/L	↑

Admitted to isolation unit

Test	Result	Interpretation
GGT	285 U/L	↑
ALT	407 U/L	↑
AST	682 U/L	↓
TP	5.7 g/dL	sl. ↓
Albumin	2.3 g/dL	sl. ↑
Hepatitis A IgM	Negative	
Hepatitis A IgG	Negative	
Hepatitis BsAg	negative	
Hepatitis BsAb	1.1	

Chemistry	Patient Result	Interpretation
Na	132	Low
K	4.6	Normal
CO2	22	High
Cl	94	Low
BUN	9.4	Very High
Creatinine	15.2	Very High
Bilirubin	12.7	Very High
Bilirubin conjugated	8.1	Very High
ALK	383	Very High
GGT	285	Very High
AST	682	Very High
ALT	407	Very High

Chemistry	Patient Result	Interpretation
Total Protein	5.7 g/dL	Slightly Low
Albumin	2.3	Low
Hepatitis A IgM	Negative	
Hepatitis A IgG	Negative	
Hepatitis B sAg	Negative	
Hepatitis B sAb	1.1 mIU/mL	
Hepatitis B core Ab	Negative	
Malaria thin smear	Negative	
Malaria thick smear	Negative	
P. falciparum Ag	Negative	
Measles IgM	Negative	
HSV PCR	Negative	

Serology	Result
Crimean Congo hemorrhagic fever	Negative
EBV VCA IgM	Positive
EBV VCA IgG	Positive
EBNA IgG	Negative

Admitted to isolation unit

Serology	Result	Interpretation
EBV VCA IgM	Positive	⇧
EBV VCA IgG	Positive	⇧
EBNA IgG	Negative	
EBV Viral Load	6.3 genome copies/mL	Massively elevated

Hematology	Result	Interpretation
WBC	19.0 x 10^3	High
Neutrophils Abs	4.37 x 10^3	Normal
Lymphocytes Abs	14.26 x 10^3	Very High
Monocytes Abs	0.38 x 10^3	Normal
Basophils Abs	0	
Hemoglobin	12.0	Normal
Platelets	138 x 10^3	Normal

Next 7 days

- Patient continued to deteriorate
- Developed the following conditions
  - Metabolic acidosis
  - Liver failure
  - Renal failure
  - DIC
  - Acute respiratory distress syndrome
  - Neurological complications

Liver Biopsy

- Submassive periportal necrosis

Diagnosis

- Epstein-Barr virus (human herpesvirus 4)
  - B cell lymphotropic gamma herpes virus
  - Infects > 90% of world population
  - Humans are only known reservoir
  - Most common manifestation
    - Acute infectious mononucleosis
      - Usually self-limiting disease of adolescents/young adults

Transmission

- Contact with infected saliva
- Infects epithelial cells and B lymphocytes
- May replicate in oropharynx before infecting B cells
- B cells infected in mucosal lymphoid tissues (tonsils)
  - Pools of memory B cells produced that circulate to other lymphoid tissues
- Infected memory B cells are long-lived
  - Low levels of viral proteins expressed; not recognized by CD8 lymphocytes
  - EBV persists for life

Symptoms of infectious mononucleosis

- Sore throat
- Fever
- Lymphadenopathy
- Faint generalized maculopapular rash

Treatment of Patient

- Corticosteroids
  - To decrease swelling in throat
  - To decrease the splenomegaly & prevent possible splenic rupture
- Patient's condition did not improve

Treatment of Patient

- Cyclosporine added
  - Recommended for patients with fulminant disease
- Patient failed to respond

Treatment of Patient

- IVIG and Rituximab (anti-CD20) added
- Patient did not respond

Final outcome

- Patient rapidly deteriorated
- No response to any therapy
- Died one week after admission

Conclusion

- No genetic testing performed
- Since patient was male, speculated that this was X-linked lymphoproliferative disease
- Family members should receive genetic testing to identify affected males and carrier females

X-linked lymphoproliferative disease (XLP)

- Rare primary immunodeficiency
- Selective inability to control EBV infection
- Probably cause of patient's condition

Affected males

- Allogenic stem cell transplant prior to EBV exposure - curative

Carrier females

- Male infants screened at birth
  - If positive, allogenic stem cell transplants performed

Case 2

My eyes cross at twilight

- Patient presentation
  - 25 y.o. female
  - Teacher
  - Pregnant
  - Complains of double vision
  - Difficulty speaking for prolonged periods of time

History

- 6 weeks ago
  - Episodes of double vision
- 4 weeks ago
  - Droopy eyelids in morning & evening
- Asthenia (lack of energy) and generalized weakness
- Symptoms exacerbated in evening

Medical history

- No allergies
- Appendectomy 10 years ago
- Medications: none
- Family history
  - Mother
    - Elevated lipids
  - Sister
    - Type 1 diabetic

Differential Diagnosis	
Brain tumor	Vertebro-basilar insufficiency
Myasthenia gravis	Multiple sclerosis
Lambert-Eaton Syndrome	Graves disease
Botulism	Chronic progressive external ophthalmoplegia
Myositis	

Physical examination

- Bilateral ptosis (drooping eyelids)
- Limitations in eye movements
- No paralysis of other cranial nerves
- Normal pupillary reflexes
- Normal reflexes in upper and lower limbs
- Normal cognition

Musculoskeletal evaluation

- Normal muscle tone
- Normal strength in lower & upper limbs

Follow-up (15 weeks later)

- 3 weeks after birth of child
- Exacerbation of diplopia and ptosis
- Limb weakness
- Difficulty swallowing
- Difficulty breathing
- Reduced muscle tone

Laboratory test results

- CBC – normal
- Electrolytes – normal
- Kidney function – normal
- Inflammatory proteins – normal
- Anti-nuclear antibody – normal
- Myositis-specific antibody - normal

Nerve stimulation examination

- >10% reduction in amplitude

Laboratory test results

- Anti-AchR – positive
- Pt result: 7.50 Normal limits: <0.5nmol/L
- Other associated antibodies – negative
  - Anti-MusK
  - Anti-LRP4

Diagnosis and Treatment

- Myasthenia gravis
- Treated with pyridostigmine
  - Patient reached minimal manifestations

Diagnosis of MG

- Based on clinical and electrophysiological data
- Suggestive symptoms
  - Diplopia, ptosis, snuffling voice, swallowing problems, muscle weakness
  - Circadian fluctuations and post-exertional aggravation

Other antibodies possible in MG patients

- Anti-MuSK (muscle specific kinase)
- Anti-LRP4 (low-density receptor-related protein-4)
  - Receptor involved in MuSK activation

Myasthenia gravis

- Characterized by fluctuating weakness of striated muscles
- Worsens with activity

Cause of weakness

- Impaired neuromuscular transmission
- Autoantibodies block acetylcholine receptors

MG pathogenesis

- Anti-Ach-R autoantibodies cause
  - Injury to neuromuscular junction through complement-mediated lysis of postsynaptic membrane
  - Blocking AChR preventing binding to ACh
  - Provoking internalization of AChR (reducing number of receptors at junction)
- Results in alteration of neurotransmission that aggravates under repetitive stimulation
  - Symptoms worsen with increased activity
  - Eyelid muscles particularly affected due to frequent eye movements

Statistics of MG

- Incidence
  - 0.3 to 2.8 per 100,000
- Prevalence
  - 700,000 patients worldwide

MG

- Can occur at any age
- Most prevalent in women under 40
- After 70 years of age, male predominance

Patient

- Developed moderate, generalized myasthenia at initial point
- After birth of son severe crisis occurred
- Trigger factors for severe crisis
  - Stress
  - Drugs
  - Infections
  - Perinatal period

MG

- Pregnancy often increases risk of crisis
- Alternation of outbreaks and remissions
- Maximal severity occurs in first 3 years in 85% of cases
- Respiratory and swallowing problems may be fatal
- Myasthenia Gravis Foundation of America
  - Clinical classification to score severity

Patient Emergency Treatment

- Admitted to ICU
- IV Immunogglobulin (IVIg)
- Non-steroidal immunosuppressive drugs
- Cholinesterase inhibitors
- Immunosupressive drugs (corticosteroids)
- Anticholinesterasics
- Plasma exchange
- Intubation not required

Patient Treatment

- After remission obtained
  - X ray and tomography
    - Mass in anterior mediastinum
      - Thymoma
    - Thymectomy performed

Thymus involvement (structural and functional abnormalities)

- Occurs in majority of MG patients
  - 15 -20% thymic tumors (thymoma)
    - Often observed after age 45-50 years
    - Thymectomy necessary
      - Does not improve MG symptoms
    - MG is generalized and more severe
      - Requires more immunosuppressive drugs

Thymus involvement (structural and functional abnormalities)

- 50-60% thymic hyperplasia (increased organ volume) or lymphoproliferative origin
  - Usually occurs in patient with early onset
    - age <45
    - predominantly women
  - Thymectomy usually recommended
    - Reduces MG severity
    - Often leads to remission and decreased concentration of anti-AChR

Patient Final Outcome

- 1 year follow-up
  - Azathioprine continued
  - Considered in complete stable remission

Child

- 10 hours after birth
  - Hypotonicity (less than normal muscle tone)
  - Poor sucking
  - No respiratory failure

Child

- Developed neonatal myasthenia
- Passive transfer of IgG antibodies to child
- Classic symptoms disappear when mother's IgG is gone
- No correlation between severity of mother's disease and onset of neonatal myasthenia

Case 3

Patient history

- 12 y.o. boy
- Taken to ER 18 hours after eye injury
- Sustained penetrating knife injury to left eye
  - Involved in fight after school
  - Stabbed by another student

Eye injury

- Minimal bleeding with some pain
  - Insisted he did not need medical attention
  - Eye was cleaned & dressed at home
- Next morning
  - Eye swollen shut; excessive bruising and pain
  - Unable to open eye
  - Complained of headache
  - Watering in uninvolved eye
  - No loss of consciousness or seizures after injury
- Parents decided to take him to ER

Past medical history

- Age 4 - tonsillectomy
- Age 6 – chicken pox; full recovery
- No other significant medical history

Family history

- Father – asthmatic on treatment
- Mother – good health
- Sibling age 8 – good health

Allergies

- none

Differential diagnosis

- Sarcoidosis
- Syphilis
- Sympathetic ophthalmia
  - Severe conjunctivitis, often purulent (pus)

Initial presentation

- Well-nourished child
- Obvious pain and discomfort
- Left eye swollen shut; periorbital bruising
- Glascow coma scale (GCS) 15/15
  - Assessment of level of consciousness
  - Performed after head injury
  - Patient: Awake, alert, cooperative

Initial presentation

- Normal vital signs
- No pallor or jaundice
- No signs of dehydration
- No lymphadenopathy
- No edema (except around injury)

Initial presentation

- No respiratory issues
- No cardiovascular issues
- No GI abnormalities
- Normal neurological function
  - Normal gait
  - Higher function intact
  - Reflexes normal

Initial presentation

- Right eye
  - No abnormalities detected
  - 20/20 vision
  - Retinal examination - no pathology noted
  - Light reflex intact

Initial presentation

- Left eye
  - Excessive bruising and swelling
  - Prolapse of iris, ciliary body and retinal tissue
  - Severely decreased visual acuity
  - Blurring
- Skin
  - No rashes

3 weeks post injury & eye repair

- Child in severe pain and discomfort
- Unable to open eyes
- GCS 15/15
  - Awake, alert and cooperative

3 weeks post injury & eye repair

- Vital signs – normal
- No pallor or jaundice
- No signs of dehydration
- Bilateral cervical lymphadenopathy
- No edema

3 weeks post injury & eye repair

- Right eye
  - Tearing and photophobia
  - Retinal epithelium
    - Large keratic precipitates and small depigmented nodules
  - Mild panuveitis
  - Decreased visual acuity - 20/200

3 weeks post injury & eye repair

- Left eye
  - Excessive swelling and pain
  - Severe panuveitis
  - Visual loss
- Cardiology
  - No abnormalities detected
- Neurology
  - No abnormalities detected

Lab results

Test	Result	Normal limits
WBC	Normal	
Hemoglobin	Normal	
Platelets	Normal	
CRP	35	0-8 mg/L
Na	Normal	
K	Normal	
Cl	Normal	
CO2	Normal	
BUN	Normal	
Creatinine	Normal	
Calcium	Normal	
Phosphorus	Normal	
Magnesium	Normal	

Lab results 3 weeks later

Test	Result	Normal limits
WBC	16	4-12x109/L
Hemoglobin	Normal	
Platelets	Normal	
CRP	85	0-8 mg/L
Na	Normal	
K	Normal	
Cl	Normal	
CO2	Normal	
BUN	Normal	
Creatinine	Normal	
HIV ELISA	Negative	
Blood culture	Negative	

CSF Cell Count

Test	Result	
PMN	0	
Lymphocytes	0	
Erythrocytes	15	
Bacteria	No growth	

Diagnosis

- Sympathetic ophthalmia (SO)
  - Rare, bilateral, non-necrotizing, granulomatous uveitis
  - Occurs after trauma or surgery to one eye and affects sight in other eye

Sympathetic ophthalmia

- Disrupted integrity of inciting eye leads to autoimmune reaction against exposed ocular antigens in injured eye as well as sympathizing eye

Treatment of patient

- Surgery performed within 24 hours of injury
- Treated with topical and systemic steroids
  - Patient was non-compliant
- 3 weeks later returned with bilateral panuveitis and loss of visual acuity

Immunology

- Eye is immune-privileged organ
  - Ocular antigens are normally sequestered within eye behind blood-retinal barrier
  - Prevents exposure to immune system
- After penetrating injury or surgery barrier is breached
  - Antigens leak into systemic environment

Immune response

- APCs recruited to site
  - Process ocular antigen and present to CD4+ lymphocytes in lymphoid tissues (lymph nodes, spleen)
  - Inflammation process stimulated
    - Complement activated
      - Opsonins generated
      - Chemotaxis occurs
      - Lysis occurs

Treatment of patient

- Removed injured eye
- Injured eye was causing sympathetic reaction in other eye
- High doses of oral prednisone prescribed

Final outcome

- Patient and parents counseled on importance of following medication guidelines
- Regular clinic visits
- Oral prednisone tapered according to therapeutic response
- Visual acuity in right eye improved from 20/200 to 20/40

Case 4

Patient Presentation

- 25 y.o. female
- Symptoms
  - For past week: swollen hands for 1 week
  - For last 2 days: swelling around eyes; shortness of breath

Patient History

- 3 weeks ago
  - Infected skin lesions on thighs
    - Treated with antibiotic ointment
- No past medical history of note
- 2 months ago
  - HIV test negative
  - No history of unprotected sex since that time
- No past surgical history

Patient History

- Allergies – none
- Medications – vitamins only
- Travel history – none
- Social history
  - Not married
  - 1 child
  - Non-smoker
  - No alcohol consumption
  - No illicit drug use

Family history

- Mother
  - Hypertension – undergoing treatment
- Father
  - No medical concerns
- 4 siblings
  - Healthy

Physical examination

- Temperature: 98.6
- BP: 160/100 (hypertensive)
- Heart rate: 85 beats/minute (tachycardic)
- Respiration: 20 breaths/minute (tachypnea)

Physical examination

- Mild conjunctival pallor
- Periorbital edema
- Bilateral edema of hands & feet
- Normal level of consciousness, alert & cooperative
- Gait, power, tone, sensation & reflexes normal
- Mild scarring from healed lesions on thighs

Laboratory findings

Test	Result	Reference Range
WBC	normal	
Hemoglobin	11.5	12.1 – 15.2 g/L
Platelets	normal	
Differential	Normocytic normochromic anemia	
BUN	38	2.5 – 6.4 mmol/L
Creatinine	780	50 – 80 umol/L
K	6.1	3.3 – 5.0 mmol/L
Phosphorus	4.0	0.8 - 1.4 mmol/L
Calcium	1.9	2.1-2.6 mmol/L
AST	1280	> 200
CO2	21	22 - 30
Anion Gap	22	10 - 15

Laboratory Findings

Serological assays	Result
CH50	Low
C3	Low
C4	Normal
Anti-DNAse B	Positive, titer 360

Laboratory Findings

Urine	Result	Reference Range
Blood	4+	Negative
Protein	2+	Negative
Dysmorphic RBCs	Present	
Oliguria	< 500 mL /24 hours	

Other findings

- Chest X-ray: fluid overload
- ECG: normal

Conclusion

- Rapidly progressive renal failure
- Glomerular filtration rate failing to normalize
- Persistent hypocomplementemia, hematuria, proteinuria

Renal biopsy ordered

- Hypercellularity of glomeruli with enlarged glomerular tufts
- Neutrophils and monocytes
- Crescent formation noted in 30% of glomeruli

Immunofluorescence

- Deposits of IgG and C3 present along glomerular capillary wall

Electron Microscopy

- Occasional patchy thickening in glomerular basement membrane
- Electron-dense immune-type deposits in glomerular basement membrane

Diagnosis

- Post streptococcal glomerulonephritis

Discussion

- Acute glomerulonephritis
  - Most common form follows infection with Group A beta hemolytic *Streptococcus*
  - Follows infection in 7-12 days
    - Allows time for antibody production

Group A *Streptococcus*

- Usually *S. pyogenes*
- Typically causes superficial infections of throat (pharyngitis) or skin (impetigo)
- Sequelae
  - Rheumatic fever (rheumatic heart disease)
  - Acute glomerulonephritis

Acute Glomerulonephritis

- *Strep* infection may cause renal complications 1-2 weeks later
  - Bacterial proteins are deposited in kidneys (nephritogenic antigens) which mediate damage to glomerular basement membrane
    - Disrupts filtering and allow antigens to cross into Bowman's space

Acute Glomerulonephritis

- Immune response follows entrapment of immune complexes in glomerular capillary membrane
- Glomerular capillary endothelial cells and mesangial cells cause swelling of capillary membrane
- Symptoms of post streptococcal glomerulonephritis occur

Symptoms

- Blood in urine (hematuria)
- Foamy urine (proteinuria)
- Fluid retention (edema)
  - Face
  - Eyes
  - Feet
  - Ankles
  - Legs
  - Abdomen
- Hypertension

Outcome

- Most cases are mild and recovery can occur
- Ongoing inflammation can result in complete and irreversible damage
  - Requires dialysis or transplant

Patient Treatment

- Goal
  - Control fluid balance and blood pressure
- Patient did not respond to diuretics
  - Pulmonary edema
  - Persistent oliguria
- Required urgent dialysis
- Continued for 3 weeks

Final outcome

- Chronic dialysis program
- Entered transplant program