Minima Medicamenta

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Minima Medicamenta

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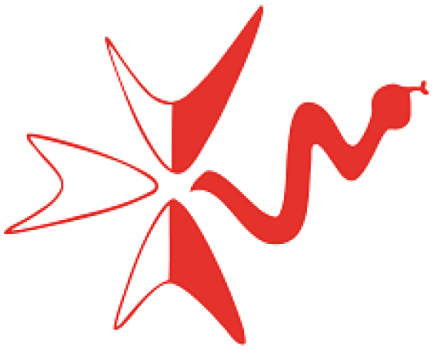

MMSA

Malta Medical Students' Association

L-Għaqda tal-Istudenti tal-Mediċina ta' Malta

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Message from the Dean of Medicine and Surgery

It is my pleasure to be writing a message once again for the publication of Minima Medicamenta, The Malta Medical Student Association (MMSA) have embarked on the fourth edition of the publication after the successful publications of three previous editions.

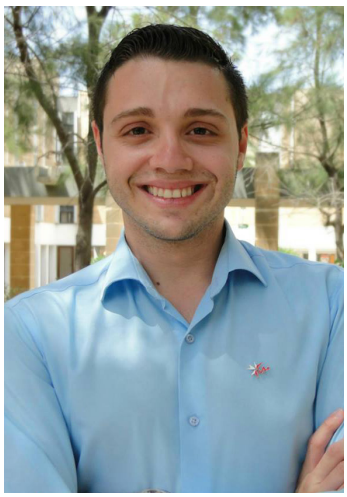
Minima Medicamenta, which is a publication recognised by the International Federation of Medical Students (IFMSA) and provides considerable educational experience looks at seven widely varying cases. For each condition, a detailed description of the relevant features in the history is given. This is followed by a systematic approach to differential diagnosis, investigations and management. A critical discussion then follows.

The collection and presentation of such unusual conditions make interesting reading. In addition, it helps the reader to learn to adopt a methodical and systematic approach to patients' problems which would be invaluable in future medical practice.

I would like to take the opportunity to congratualte the individual contributions as well as the MMSA organisation for this continuing activity. In addition, I would also like to thank my colleague mentors who have acted as experienced guides for the students concerned.

Professor G. LaFerla
Dean, Faculty of Medicine and Surgery

Message from the President of the Malta Medical Students' Association



We frequently associate the teaching curriculum with a fixed, immalleable programme, which dictates what a student should learn and what is indisputably unnecessary. I find that the study of medicine exquisitely opposes this bleak mindset: a doctor should always know that he never knows enough.

It is up to each and every medical student to pursue his or her own fountains of knowledge. And being at the forefront of medical care, the patient is the pinnacle of this clinical pursuit.

This publication undoubtedly represents the epitome of proactivisim, diligence and initiative in a student's life. It celebrates the willingness of each medical student in learning from the patient, in discussing a history, in professionally writing a comprehensive summary of the information collected, and in presenting them fluently to tutor and patient alike.

Minima Medicamenta is testimony to what our association promotes: an inquisitive mind within an everchanging medical environment.

I truly wish all students, both authors and readers, to cherish the spirit behind this publication and to use it to further their own thirst for the pursuit of medical knowledge.

Gabriel J. Ellul
MMSA President 2014-2015
Malta Medical Students' Association

Message from the Malta Medical Students' Association Medical Education Officer

This is your publication, a publication made by medical students for medical students. The Standing Committee on Medical Education (SCOME) aims to gather people who are enthusiastic about their own education and together, strive to improve it. One aspect which medical students have little exposure of is research. We hear a lot about research and evidence based medicine however, little do we learn about how we can improve the research available and make use of it in our studies. SCOME aims at offering students the opportunity to participate and explore this area of medical education.

This is the fourth edition of SCOME's main publication Minima Medicamenta. This publication is not only important for the authors who make the most of this opportunity to develop and improve their skills in reading and writing up research publications, but also for the readers who will be learning about interesting cases that they might have missed during hospital rotations.

I would like to sincerely thank the coordinators Maria Grazia Grech and Isaac Bertuello who were extremely dedicated and motivated to work with the SCOME team towards this project. I would also like to thank everyone who was involved for their constant efforts and hard work to produce such a professional and successful publication.

I hope you readers will make the most of it!

Sarah Catania
MMSA Medical Education Officer 2014-2015
Malta Medical Students' Association

Message from the Editors

Minima Medicamenta is now its fourth year of publication. This year we have seven cases from different specialties including surgery, haematology and trauma.

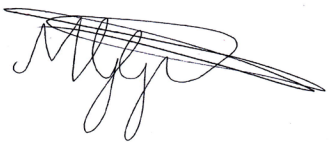
As in previous editions, the aim of this publication is two fold. It is a journal which helps students publish themselves. This in turn enables them to hone their skills in scientific writing, something which is very important today, when research and sharing of information are becoming of paramount importance in the world of medicine.

The second aim is to provide a resource for learning for the rest of the students. We aim to help share information about rare diseases or unusual presentations of commoner ones to allow students to gain new insight into a subject they may not have encountered in that much detail before.

We would like to extend our appreciation to all those who helped make this publication possible. Firstly we would like to thank Gabriel J. Ellul, the President of the Malta Medical Students' Association (MMSA) and Sarah Catania, the Medical Education Officer. We would also like to thank the MMSA PRO team, the proofreader Stephanie Vella and the cover designer David Borg. Last but not least, we would like to thank all the students who participated and wrote the cases and the doctors who supported them throughout.

We hope you find this publication instructive and useful.

Isaac Bertuello
Minima Medicamenta Editor 2015
Malta Medical Students' Association



Maria Grazia Grech
Minima Medicamenta Editor 2015
Malta Medical Students' Association

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Case Number 1
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Michelle Boffa & Daniel Borg
Reviewed by: Dr. Maria Mallia, Consultant Neurologist

Case summary:

Demographic details:
Mr. AB, male, Birkirkara
Referred from: Orthopaedics

This previously healthy, right-handed, 61-year-old, gentleman presented with a history of weakness that resulted in a number of futile nerve release procedures in an attempt to alleviate symptoms that were initially thought to be due to nerve entrapment. The muscle weakness, most prominent in both upper limbs, especially his left hand was accompanied with left intrinsic hand muscle wasting and some paraesthesia in the left fingertips. Marked hyporeflexia was also present. Neurological investigations led to the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) being established

Presenting complaint:

Slowly progressive bilateral weakness in the upper limbs, particularily marked in his left hand.

History of presenting complaint:

This weakness was first noticed back in 2002 while the patient was having supper with his family and was unable to grip his fork.

Over the course of the years, his weakness progressed, gradually depriving him of significant power in his left hand. On presentation the patient had marked muscle wasting in his left (non-dominant) hand. Additionally, the patient also had muscle twitching in both upper limbs and frequent muscle cramps in his thigh and calf muscles bilaterally when lying immobile for long periods.

He had some paraesthesia in the fingertips of his left hand and numbness in both upper limbs on prolonged flexion of the elbows. Oherwise, no other sensory deficits were noted. The patient's condition never caused him any pain. His symptoms showed no fluctuation during the day and his sleep was not impaired in any way. A week ago, the patient had an isolated episode of sudden unsteadiness whilst walking.

He denies any stiffness in his wrist and finger joints. He also denies having any loss of consciousness, vertigo, diplopia, dysarthria, dysphasia or dysphagia. The patient is alert, responsive and ambulant without the need for walking aids. He has no problems with speech and eats well without choking.

Past medical and surgical history:

Past medical history:

- Mild hypercholesterolaemia which is controlled by diet and exercise.
- Hypothyroidism which is controlled with replacement therapy.

Negative for: - Diabetes Mellitus
- Hypertension

Past surgical history:

- Anal stretch for anal fissure.
- Right knee replacement.
- Left carpal tunnel and left cubital tunnel release.

Drug history:

No known drug allergies.
The patient is compliant with his medication and does not complain of any side-effects.

Drug Name (Generic)	Dosage	Frequency	Type	Reason
Levothyroxine	100 µg	Daily	Thyroid hormone replacement	For hypothyroidism

Family history:

Paternal cousin has congenital monoparesis. None of the patient's seven siblings have any neuromuscular problems. His mother died of a myocardial infarction and his father died due to colon cancer.

Social history:

A married, non-smoking, boarded out gentleman. He used to work in construction but had to change his job due to his condition and now works as a watchman. He drinks occasionally and walks on a regular basis. The patient is completely independent although his weakness does make his activities of daily living more labourious. He lives with his wife and daughter. He can drive an automatic car safely.

Systemic inquiry:

- General Health: Looks well in general; no weight loss or diminished appetite noted
- Cardiovascular System: Nil to note
- Respiratory System: Nil to note
- Gastrointestinal Tract: Nil to note
- Genitourinary System: Nil to note
- Central Nervous System: See above
- Musculoskeletal System: Nil to note
- Endocrine System: Nil to note

Discussion of results of general and specific examination:

Upper limbs:

Inspection
Fasciculations in right upper arm.
Asymmetry between right and left; complete wasting of the left intrinsic hand muscles, mild clawing in the left hand. Froment's sign in the left hand.
Scars of cubital tunnel release and carpal tunnel release.

Tone
Normal bilaterally

Power (MRC grading)

	Right	Left
Deltoid	5/5	5/5
Biceps brachii	5/5	5/5
Triceps brachii	5/5	5/5
Wrist extension	5/5	4/5
Wrist flexion	5/5	4/5
Finger extension	5/5	2/5
Abductor pollicis brevis	4/5	0/5
Abductor digiti minimi	4/5	0/5
Finger adduction	4/5	2/5

Sensation
Normal throughout

Reflexes (tested with Jendrassik maneouvre):
Biceps brachii, triceps brachii and brachioradialis were all hyporeflexic (bilaterally)

Lower limbs:

Inspection
No wasting
No fasciculations
Knee arthroplasty scar on right knee
Can stand on toes and heels

Tone
Normal bilaterally

Power (MRC grading)

	Right	Left
Hip flexion	5/5	5/5
Hip extension	5/5	5/5
Knee extension	5/5	5/5
Knee flexion	5/5	5/5
Ankle dorsiflexion	5/5	5/5
Big toe dorsiflexion	5/5	5/5
Ankle plantar flexion	5/5	5/5

Sensation
Normal throughout

Reflexes
Knee and ankle jerk were both hyporeflexic
Gait
Normal

Differential diagnosis

- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Amyotrophic Lateral Sclerosis (ALS) / Motor Neurone Disease (MND)
- Multifocal motor neuropathy with conduction block
- Paraneoplastic syndrome
- Polyneuropathy secondary to a paraproteinaemia
- Vasculitic polyneuropathy
- Radiculopathy (but usually not bilateral)
- Motor neuropathy secondary to lead (Pb) poisoning
- Diabetic peripheral neuropathy
- Hereditary peripheral neuropathy
- Old polio

Diagnostic procedures:

Laboratory exams:

Test: Thyroid function tests, Liver function tests and Blood Glucose level
Justification for test: Looking for metabolic/biochemical causes.
Result: Normal.
Conclusion: Metabolic/biochemical causes not implicated.

Test: Erythrocyte Sedimentation Rate
Justification for test: Looking for evidence of extensive inflammation.
Result: 11mm; not elevated.
Conclusion: No evidence of systemic inflammation.

Test: B12 and folate levels
Justification for test: Looking for deficiency.
Result: Within range.
Conclusion: Not deficient.

Test: Serum Immunoglobulin analysis
Justification for test: Looking for evidence of a polyneuropathy due to a paraproteinaemia.
Result: No monoclonal band present.
Conclusion: The neuropathy is probably not due to a paraproteinaemia.

Test: Vasculitic screen
Justification for test: Looking for evidence of a vasculitic polyneuropathy.
Result: Negative.
Conclusion: The cause is probably not a vasculitic polyneuropathy.

Test: Tumour markers
Justification for test: Looking for evidence of a neoplasm.
Result: Negative.
Conclusion: The cause is most likely not a paraneoplastic syndrome.

Test: Antiganglioside antibodies (anti-GM1)
Justification for test: May indicate evidence of a multifocal motor neuropathy with conduction block.[1]

Result: Mildly elevated.
Conclusion: Multifocal motor neuropathy may be present.

Test: Lumbar Puncture
Justification for test: Looking for abnormal CSF analysis.
Result: Normal, however, the protein level was on the high side of the normal range (borderline).
Conclusion: The fact that the protein level was borderline high might indicate an inflammatory polyneuropathy.

Instrumental exams:

Test: Electromyography (EMG)
Justification for test: Looking for abnormalities in neuronal conduction.
Result: Consistent with generalised demyelinating sensory motor polyneuropathy with secondary axonal change and denervation in the muscles tested.
Conclusion: Polyneuropathy confirmed.

Therapy:

Drugs:

Drug Name (Generic)	Dosage	Frequency	Type	Reason
Intracet® (IVIG)	0.4mg/kg	For five days	IV	CIDP responds to IVIG

Diagnosis:

The slowly progressive course of the symptoms and signs indicate that the problem at hand is a chronic one. Symptoms were generalised in affecting various parts of the body, namely the upper and lower limbs with motor weakness being the main feature, together with a slight sensory impairment (paraesthesia noted in the history, however normal sensation on examination) and markedly diminished tendon reflexes. This points towards a generalised problem of lower motor neuron pathology. Thus a polyneuropathy should be considered. Furthermore, the patient suffered from a fall recently which might reflect impaired coordination or possible autonomic nervous system involvement resulting in dizziness (since lower limb power is normal).

At this point, the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) should come to mind. Many consider a duration of symptoms for more than 8 weeks to be adequate for diagnosing the condition[2]. Investigations ruled out important differentials, and the fact that the patient was found positive for anti-GM1 antibodies increases the likelihood of a multifocal motor neuropathy being present. EMG changes were typical of what one would expect in CIDP, thus confirming the diagnosis.

Final treatment and follow ups:

The immunoglobulin course was five days long and during the first few days of treatment the patient was already experiencing some improvements in motor function of his upper limbs. Subsequently the patient was to have a number of outpatient sessions for IVIG pulses and follow-up at MOP where the improvement was to be confirmed clinically.

Fact Box 1

Title: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP is the most common treatable chronic neuropathy in the western world. This autoimmune polyradiculoneuropathy is acquired over a period of 2 or more months and typically targets the peripheral nervous system (PNS) proximally, with involvement of nerve roots and major plexuses.

Clinicl Features: The natural course of CIDP is that of a progressive or relapsing condition, with predominant symmetrical motor deficits occuring in a proximal to distal pattern. Other presentations of CIDP include evolution from a subacute monophasic path or, rarely, as the acute Guillain-Barre' syndrome (GBS), only to be followed by progression of the disease or relapse. Hypo- or arfelexia is a feature since this is a lower motor neuron disorder[3,4].

Risk factors: Family history

Diagnosis:

- Appropriate clinical features
- Demyelinating picture on electrophysiological studies, as specified by the EFNS and PNS Task Force (2010) criteria, which request proof of any of the features listed below in at least 2 nerves:
- Prolongation of distal latency
    - Reduction in motor conduction velocity
    - Prolongation of F wave latency
    - Absence of F waves
    - Partial conduction block
    - Abnormal temporal dispersion
    - CMAP reduction in amplitude

- Additional features to back the diagnosis

Raised CSF protein and normal leucocytes

- Nerve root or plexus hypertrophy as evidenced by gadolinium enhancement on MRI
- Primary demyelination on nerve biopsy
- Amelioration with immunotherapy

Pathogenesis:

The endoneurium and perivascular regions are invaded by T (CD4 & CD8) and B lymphocytes as well as macrophages, which together orchestrate phagocytic demyelination. Of note is the high expression of MHC on Schwann cells and the increasingly leaky blood nerve barrier (BNB) [5, 6,7] . The inadequately high permeability of the BNB to autoantibodies derives from T-cell transmigration occurring through interaction of T-cell adhesion molecules VLA-4 and LFA-1 with their counterparts VCAM-1 and ICAM-1 on endothelial cells, in association with chemokines, cytokines and matrix metalloproteinases. As a result, nodal and paranodal sites lose their structural integrity with concomitant early conduction block[8,9].

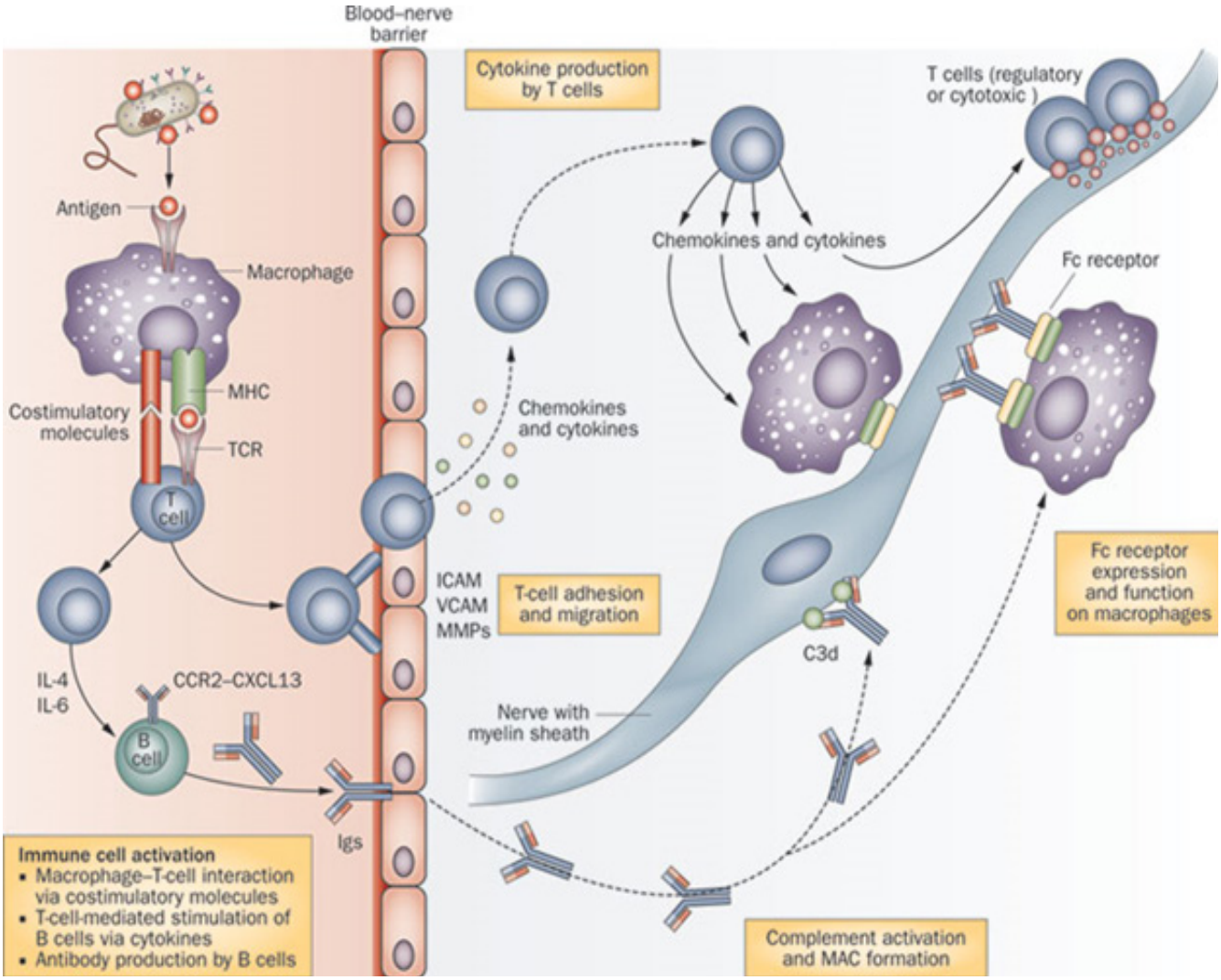

Figure 1: Immunopathology of CIDP

Treatment: A variety of treatment options exist, the best of which is chosen on the grounds of efficacy, cost, availability and safety[3].

One suggested approach to treatment involves administering IVIg as first line, particularly in patients with pure motor CIDP (in whom corticosteroids can aggravate the condition) [10]. In case of resistance, plasmapheresis would be the next option. If the patient still does not respond, a combination of a corticosteroid and immunosuppressives is tried. The mentioned treatment options provide short-term resolution, hence they must be supplemented by a maintenance course of IVIg.

Whichever treatment is opted for, patients on the road to remission should be put on lower doses or have their treatment withdrawn completely since it is known that a substantial number of patients need no long-term maintenance therapy [11, 12, 13] .

Early recognition of the disease and adequate treatment can help prevent debilitating and disabling outcomes.

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Case Number 2
GM1 Gangliosidosis

Ritianne Buhagiar and Ayrton Borg
Reviewed by Dr. Simon Mifsud

Case summary:

Demographic details:
Mr. JB, male, Xaghra
Referred from: Home due to family history

Mr. JB is a two-year-fourth-month old Caucasian boy from Xaghra. He is a known case of GM1 gangliosidosis. This child is a type 1, meaning early onset (presenting in the early months of life). The condition is characterised mainly by neurodegeneration and regression of achieving milestones, decreasing muscle activity and seizures. He was breastfed during his first year of life but he then started demonstrating oral feeding problems and began losing weight, necessitating nasogastric tube feeding. A soft silicone nasogastric tube was inserted in his right nostril, and requires changing every 6 weeks. This ensures adequate hydration and nutrition. He is now suffering from recurrent respiratory tract infections and was thus admitted for hospitalisation. Medications are also administered through the nasogastric tube in order to reduce the risk of aspiration pneumonia.

Presenting complaint:

The child presented with signs and symptoms suggestive of a lower respiratory tract infection:
Tachypnoea
Fever
Yellowish sputum production
Tachycardia

History of presenting complaint:

For the last 6 months, he has had recurrent episodes of respiratory tract infections requiring antibiotics and recurrent hospitalisations especially after the age of 23 months.

Past medical and surgical history:

Past medical history:

Given the family history, when the patient was born, there was a high index of suspicion for GM1 gangliosidosis and the diagnosis was confirmed by one week after gene testing for the enzyme beta-galactosidase. As a baby, he was asymptomatic. He appeared normal in the first three months during regular surveillance checks. In fact, after being diagnosed with this condition there was a period of denial in which the parents could not believe that their child had this condition. But on subsequent monthly check-ups, it was observed by the paediatricians who examined him regularly that he failed to achieve the expected skills in important developmental milestones including head lag by 3-4 months, lack of ability to roll over by 7-8 months and lack of ability to sit unsupported by 10 months. Also, after the age of 9 months, there was gradual increasing hypotonia and decreased interaction with his carers. He lost his eyesight after 17 months of age due to progressive accumulation of toxic metabolites in the cerebral cortex.

Drug history:

No known drug allergies. Compliant with the National Immunisation Service; the child was vaccinated against Diphtheria, Tetanus, Pertussis, Polio, Haemophilus and Hepatitis B. He also received the Pneumococcus vaccine and last year was vaccinated against Influenza.

Drug	Dosage	Frequency	Type	Reason
Cephalexin	125mg	8 hourly for 7 days	Cephalosporin antibiotic	To eradicate bacterial infection

Co-amoxiclav was also given to eradicate Pseudomonas aeruginosa.

Family history:

His brother died from cardio-respiratory failure resulting from GM1 gangliosidosis at the age of 2 years and 3 months. The condition was much more severe in his brother and the symptoms were present earlier. He had head lag from the very beginning and made no eye contact with carers; he never smiled or reacted socially. He spent almost all his life in hospital, suffering from recurrent respiratory tract infections. Both parents were referred for genetic testing and counselling and both were shown to be carriers of this condition.

Social history:

The patient has three older brothers. In the beginning, he used to smile at them and laugh but his social interactive skills began regressing after 6 months of age.

Systemic inquiry:

- General health: Healthy skin but cachectic and lethargic.
- Cardiovascular system: Tachycardia at 160 beats per minute.
- Respiratory system: Respiratory distress with chest wall recessions, expiratory wheeze, inspiratory crackles and respiratory rate of 55 breaths per minute.
- Gastrointestinal System: Feeds given via nasogastric tube.
- Genitourinary system: Nil to note.
- Central nervous system: Generalised decreased movement.
- Musculoskeletal system: See above.
- Endocrine System: Nil to note.

Current therapy:

Non-pharmacological treatment:
Physiotherapy is the mainstay of therapy focusing on facilitating clearance of upper respiratory tract secretions. This is done twice a day by a physiotherapist and more frequently by the caring mother.

When the patient is short of breath, particularly during prolonged seizures, which cause the oxygen saturation to decline below 90%, oxygen is administered via nasal prongs or facemask in order to improve oxygenation.

When there are rattling breathing sounds, a sterile suction catheter is passed from the mouth and oropharynx so as to clear out secretions. The mother applies external tracheal pressure at times to encourage the cough reflex. The patient is at times placed in a 20^{o} head down position for postural drainage of lung

secretions. This is carried out around three times daily.

A soft silicone 8mm nasogastric tube is replaced every 6 weeks for feeding. Food is given in liquidised form. The patient is fed 90ml every 3 hours, skipping the 3am feed. Medication is also administered through this tube.

In order for the nasogastric tube to be inserted, the distance between the bridge of the nose to earlobe and the distance from the bridge of the nose to the xiphoid process are measured and added. The distance in this case is around 31cm, however to ensure that the tube inserts well in the stomach, 33cm of tubing is used. Before feeding, a syringe is attached to the free end of the tube and gastric contents are aspirated. Subsequently a pH indicator is used which should turn red due to gastric acidity, thus ensuring that the nasogastric tube been appropriately positioned in the stomach.

Blood was obtained from the infant either during cannula insertion or in the first few days from the cannula itself or via the 'Broken Needle Technique' (i.e. breaking the hub off the needle).

In order to perform the latter, the catheter was secured by applying light finger pressure on the catheter beyond the cannula. Then, the cannula was withdrawn slowly. The cannula was peeled apart whilst maintaining forward pressure on the catheter, taking care not to dislodge the catheter from the vein. Following venipuncture, the catheter was advanced through the breakaway needle and the needle was withdrawn from the vein. The needle wings were pinched firmly together to initiate breaking of the needle. Then, the needle was peeled smoothly until the needle halves were held together only at the tip. Finally, the catheter was carefully lifted out of the needle lumen.

This technique is ideal because the venipuncture hole is smaller than a cannula, thus preserving the infant's tiny veins.

Drugs:

Drug Name (Generic)	**Dosage**	**Frequency**	**Type**	**Reason**
Clonazepam	0.25mg	Once daily	Anticonvulsant	To regulate seizures
Sodium Valproate	8ml	12-hourly	Anticonvulsant	To regulate seizures
Lactulose	2-5ml	PRN	Osmotic laxative	To reduce constipation
Salbutamol (nebulizer)	0.4ml	PRN	Bronchodilator	To treat bronchospasm
Nebulized Hypertonic Saline (3%)	4ml	12-hourly prior to physiotherapy	Mucolytic	To enhance mucus clearance from chest
Bromhexine	2ml	8-hourly	Mucolytic	To enhance mucus clearance from chest

Discussion of results of general and specific examinations:

On observation, the skin of the patient appeared healthy but he was cachectic. On examination, he had significant head lag and a retracted right tympanic membrane (chronic). With regards to facial features, he had frontal bossing and a flat nasal bridge. Paucity in movements was noted in his face, upper and lower limbs. Generalised seizures were observed which mostly consisted of eye and mouth twitching and occasional increased tone in his upper and lower limbs. For the past few days, he also had fever and

yellow respiratory tract secretions.

Unlike 50% of the infants with lysosomal storage diseases, this particular child showed no macular cherry-red spot on fundoscopy.

Hepatosplenomegaly – liver and spleen measure 7cm and 3cm respectively.

Heart rate increased at 160 beats/minute (normal <120).

Breathing rate of 55 breaths/minute (normally <30), chest wall recessions and respiratory distress.

Differential diagnosis:

- GM1 Gangliosidoses
- GM 2 Gangliosidoses
- I-cell Disease (Mucolipidosis Type II)
- Mucopolysaccharidosis Type IH
- Mucopolysaccharidosis Type IV
- Sialidosis (Mucolipidosis I)
- Wilson disease

Diagnostic procedures:

For GM1 gangliosidosis:

Laboratory exams:
Test: Peripheral blood film.
Justification for test: To test for a lysosomal storage disease.
Result: Vacuolated lymphocytes were observed under the microscope.
Conclusion: A lysosomal storage disease is highly probable.

GM1 gangliosidosis is suspected because Morquio type B syndrome has a later age of onset.

Test: DNA testing on newborn venous sample (This is a specific test for this condition.).
Justification for test: To identify the gene deletion that leads to a deficiency of beta-galactosidase.
Result: GLB1 gene deletion is observed on the short arm of chromosome 3 of white blood cells.
Conclusion: This gene that provides instructions for beta-galactosidase enzyme synthesis is lacking, hence GM1 gangliosidosis is confirmed.

For the respiratory tract infection:

Test: Complete Blood Count.
Justification for test: As a baseline; repeated on several days afterwards to monitor progression.
Result: See next page.

Test	*Result*	*Reference interval*	*Units*
Sodium, serum	132	135-145	mmol/L
Potassium, serum	4.5	4.1-5.3	mmol/L
Albumin, serum	34	35-55	g/L
Urea	1.6	4.0-8.2	mmol/L
WBC	6100	4000-10,500	x109/L
Neutrophils	3600	3000-5800	x106/L
Lymphocytes	1600	1500-3000	x106/L
Platelets	284	150-400	x109/L
Haemoglobin	10.9	13.0-18.0	g/dL

Conclusion: Low white blood cell count lead showed that there was a high risk of infection. This low white blood cell and platelet count was due to splenomegaly. Low haemoglobin indicates anaemia. Slightly low sodium indicates fluid retention.

Test: C-reactive protein test.
Justification for test: To assess if there is an inflammatory process.
Result: 36mg/L (normal: <13mg/L).
Conclusion: The elevated concentration of C-reactive protein confirms the presence of an inflammatory process.

Test: Blood Cultures.
Justification for test: To detect the presence of bacteria or fungi in the blood.
Result: No bacteria or other organisms were grown.
Conclusion: No bacteraemia is present.

Test: *Sputum Culture.*
Justification for test: To identify the microorganism causing the infection.
Result: *Haemophilus influenzae* was cultivated.
Conclusion: This is probably the cause of fever so antibiotics could be used.
Beforehand, *Pseudomonas aeruginosa* was cultivated in his tracheal secretions.

Therapy:

The physiotherapy sessions are not tolerated since the child is severely affected by the chest infection. At the moment, in view of the respiratory distress, feeds are decreased to 75 ml and might be stopped to minimise gastric distension and splinting of the diaphragm.

Drugs:

Drug	**Dosage**	**Frequency**	**Type**	**Reason**
Ceftazidime	275mg	8 hourly for 7 days	Antibiotic	To eradicate *Haemophilus influenzae*

Diagnosis:

The medical team is also discussing with the parents whether to give the child the influenza vaccine while he is feeling a bit better or to make use of cocooning i.e. vaccinating the people in close contact with the child instead of vaccinating the child himself. Moreover he was not given the MMR vaccine, which is usually given at 16 months of age, because it might constitute as extraordinary treatment given that he

will not be attending school.

Final treatment and follow up:

He was given a 2 week course of intravenous benzyl penicillin and gentamicin and was advised to continue benzyl penicillin for 2 weeks prophylaxis. The patient was given an appointment to be followed up at 'Grown-ups with congenital heart defects' clinic.

Diagnosis:

The patient was diagnosed with infantile GM1 gangliosidosis. This subtype combines the features of a neurolipidosis (i.e. neurodegeneration, macular cherry-red spots) with those of a mucopolysaccharidosis (i.e. visceromegaly, dysostosis multiplex, coarsened facial features). This form of GM1 gangliosidosis most frequently presents in early infancy and may be evident at birth. Once these symptoms and signs are identified, the patient is referred for genetic testing and counselling which is specific for this particular condition.

A current respiratory tract infection was diagnosed through positive sputum cultures, an elevated CRP and response to intravenous antibiotics.

Final treatment and Follow-up:

Currently no effective medical treatment is available for the underlying disorder in patients with GM1 gangliosidosis. Patients with this condition normally die with pneumonia or cardio-respiratory failure. The life expectancy is between 18-24 months. However, luckily enough, due the continuous care of his parents, this child is now 28 months old. Unlike Gaucher's disease which is also a lysosomal storage disease, there is no enzyme therapy for GM1 gangliosidosis. Reportedly a girl with infantile/juvenile GM1 gangliosidosis successfully underwent a bone marrow transplant as soon as she was diagnosed with the condition before any symptoms started to occur. However, it was shown that this transplant was of no long-term benefit.

Fact Box 2:

Name of Condition: Infantile GM1 Gangliosidosis

Infantile GM1 Gangliosidosis is an autosomal recessive disease in which the enzyme β–galactosidase is deficient. This disease is quite rare, and its prevalence at birth is thought to be 1: 100,000–200,000 live births[5], however an unusually high prevalence of one per 3700 live births has been reported in Malta [3, 5]. The cause of infantile GM1 gangliosidosis is a mutation in the gene GLB1 located on the chromosome band 3p21.33 [3].
β–galactosidase is an enzyme which is found in lysosomes. Its action is to remove the terminal galactose subunit from compounds which have it attached to them. These compounds include GM1 gangliosides (commonly found in neurones) and keratan sulfate[3]. This leads to the accumulation of these compounds since they will not be degraded, leading to the various symptoms of the disease.

Signs and symptoms:
Symptoms of infantile GM1 gangliosidosis include hepatosplenomegaly, generalised skeletal dysplasia, coarse facial features and progressive central nervous system degeneration. Macular cherry–red spots have also been reported in about 50% of cases [6, 3].

Risk factors:
Once the parents have a child with this condition, they will be referred for genetic testing and a positive result would confirm that they have a recurrence risk of 1 in 4 (25%) for each unborn child. Males and females are equally likely to be affected. There is also a 2 in 4 (50%) chance for each child to be heterozygous for the condition i.e. they will not be affected by the condition but are carriers, and a 1 in 4 (25%) chance that the child will be neither affected nor a carrier.

Diagnosis and management:
GM1 gangliosidosis can be diagnosed by analysing the activity of β–galactosidase using biochemical analysis. The enzyme is obtained from leukocytes in the blood. However this diagnosis cannot be used to diagnose carriers of this condition. Molecular sequence analysis of the GLB1 gene is another technique used to diagnose GM1 gangliosidosis patients [4, 1]. Amniotic fluid may also be used to diagnose this condition antenatally [2].

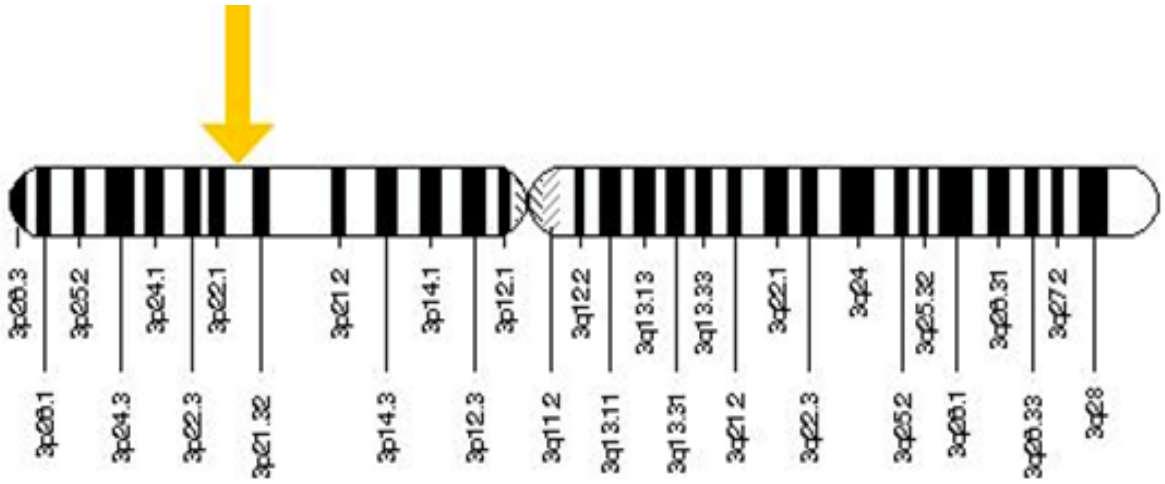

Figure 1: This shows the location of the GLB-1 gene

Unfortunately there is no curative treatment for this disorder. Bone marrow transplantation in an individual showed no long–term benefit. Presymptomatic cord-blood haematopoietic stem-cell transplantation has been suggested as a possible treatment as it has shown success with other lysosomal storage disorders [3].

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Case Number 3
Prune Belly Syndrome aka Eagle-Barrett Syndrome

Melanie Grima and Nicola Mallia
Reviewed by: Dr Valerie Said Conti MD MRCPCH FRCPCH DCH

Case summary:

HM, male

Severe bilateral hydronephrosis was noted at 20 weeks gestation with normal liquor at the time. The baby was delivered by elective C-section at 39 weeks gestation and very little liquor was noted. He was noted to have deficient abdominal wall musculature and cryptorchidism and prune-belly syndrome was suspected. A renal US confirmed bilateral severe hydroureteronephrosis with no evidence of posterior urethral valves or vesico-ureteric reflux on micturating cystourethrogram. A DTPA scan excluded outflow tract obstruction and a DMSA scan showed a non-functioning left kidney. His creatinine was noted to be 228umol/l (normal creatinine at this age 20-30umol/l). An ultrasound of the brain and back revealed no spinal anomalies and an echocardiogram showed a normal heart. Over the first few months of life he was managed conservatively on medications for chronic kidney disease. At the age of 1 year he underwent a left orchidopexy and a right first stage Fowler Stephen's procedure. The second stage was performed a few months later.

Presenting complaint:

Patient admitted to undergo left open nephrectomy.

History of presenting complaint:

HM presented a few weeks earlier, at 18 months of age, with a pyonephrosis of his non-functioning left kidney. A left nephrostomy was urgently performed to drain the pus. He received 2 weeks of intravenous antibiotics and was readmitted for a left nephrectomy.

Past medical and surgical history:

Past medical history:
Chronic kidney disease, Stage 4 (baseline creatinine 180umol/l).
Gastro-oesophageal reflux

Past surgical history:
Left orchidopexy, right first stage Fowler Stephen's procedure, circumcision (February 2014).
Second stage right Fowler Stephen's procedure complicated by acute kidney injury secondary to acute urinary retention from right ureteric obstruction. Right ureterostomy performed (August 2014).

Drug history:

Drug	Dosage	Frequency	Type	Reason
Calcium carbonate	120mg (2mls)	Four times a day	A dietary supplement	To maintain electrolyte balance
Sodium bicarbonate	5mmols	TDS	Antacid	Reduces stomach acid
Sodium chloride	4mmol	BD	A dietary supplement	To maintain electrolyte balance
Ranitidine	12mg (0.8mls)	TDS	Histamine-2 blocker	To reduce the amount of acid in the stomach
Sytron	3mls	BD	A dietary supplement, to increase levels of iron	The increase in iron stimulates erythropoiesis
Alfacalcidiol	300nanog	Daily	A dietary supplement, an analogue of vitamin D	To increase the levels of calcium.
EPO beta	500 units	Weekly	A recombinant form of erythropoietin and therefore stimulates erythropoiesis	To stimulate erythropoiesis
Co-amoxiclav	78mgs nocte	Four – six times a day	Anti-biotic	To treat any urinary tract infections

No known drug allergy.

Family history:

No relevant renal or other problems.

Social history:

Lives at home with his two parents.

Systemic inquiry:

- General Health: Nil to note
- Cardiovascular System: Nil to note
- Respiratory System: Nil to note
- Gastrointestinal System: Nil to note
- Genitourinary System: As discussed above
- Central Nervous System: Nil to note
- Musculoskeletal System: Weak abdominal muscles
- Endocrine System: Nil to note
- Others: Nil to note

On examination:

- Afebrile
- Heart sounds S1 and S2
- Clear chest

- Abdomen soft, weak abdominal musculature, non-tender – left nephrostomy clean, not erythematous, right ureterostomy pink, healthy mucosa. No organomegaly. Bowel sounds normal.
- Genitalia normal male, testes both in scrotal sac.

Discussion of general and specific examination:

The report illustrates the case of an 18 month old boy who was noted to have bilateral hydroureteronephrosis antenatally which was confirmed post-natally. The presence of deficient abdominal wall musculature, cryptorchidism and renal problems led to the suspicion of prune belly syndrome. He required bilateral orchidopexy as well as a circumcision to minimise urinary tract infections. The non-functioning left kidney was complicated by a pyonephrosis and required urgent removal. His creatinine improved in the first months of life, as is the norm as the kidneys mature, and settled at 180umol/l (chronic kidney disease stage 4). Optimisation of nutrition and medical correction of biochemical abnormalities will help to ensure normal growth and development.

Differential diagnosis of antenatal bilateral hydronephrosis:

- Bilateral vesicoureteric reflux
- Posterior urethral valves in males
- Bladder outlet obstruction
- Megacystis microcolon intestinal hypoperistalsis syndrome[1]

Major Causes of Antenatal Renal Tract Dilatation[2]

• Transient hydronephrosis (normal postnatal scan)	50%
• Hydronephrosis with no evidence of obstruction; or extrarenal pelvis	15%
• PUJ obstruction	11%
• VUR	9%
• Megaureter (obstructed, refluxing, non-refluxing and non-obstructed or both refluxing and obstructed)	4%
• Renal dysplasia	3%
• MCDK	2%
• Duplex kidney +/- ureterocoele	2%
• PUV	1%
• Others	5%

Diagnostic procedures:

Test: Bloods

Haemoglobin	9.5 g/dl to detect anaemia of chronic disease
Haematocrit	30 %
White cell count	11.5 $x10^9$/l
Neutrophils	7.2 $x10^9$/l
Lymphocytes	3.16 $x10^9$/l
Reticulocytes	42.5 $x10^9$/l
Platelets	208 $x10^9$/l
Ferritin	120 ng/ml (28-365) to assess iron stores in CKD

Sodium	134 mmol/l
Potassium	4.99 mmol/l to exclude hyperkalaemia in CKD
Chloride	100.9 mmol/l
Urea	14.9 mmol/l to exclude uraemia
Creatinine	166 umol/l biomarker for renal function
Bicarbonate	22.4mmol/l to exclude acidosis
Bilirubin	2.4 umol/l (1.72-17.1)
Gamma glutamyl transferase	9 U/L (8-61)
ALT	9 U/L (5-41)
Alkaline phosphatase	167 U/L (0-300) to assess bone mineral disorder
Albumin	44.9 g/l (34-48)
Calcium	2.58mmol/l (2.15-2.55) to assess bone mineral disorder
cCalcium	2.48 mmol/l (2.05-2.6)
Phosphate	1.92 mmol/l (0.87-1.45) to assess bone mineral disorder
Magnesium	0.99 mmol/l
PTH	107+ pg/ml (15-65) to assess bone mineral disorder
Total 25 (OH) Vitamin D	51 ng/ml to assess bone mineral disorder

Imaging Tests:

Test: Ultrasound in utero
Justification for test: To detect congenital defect.
Result: Left kidney: Grade IV hydronephrosis with cortical thinning 1.5mm with no hydroureter. Right kidney with grade III hydronephrosis with megaureter down to urinary bladder. No ureterocoele identified. Bladder contains moderate amount of fluid. No free fluid.
Conclusion: patient has antenatal bilateral hydronephrosis.

Test: Ultrasound Scan of kidneys
Justification for test: To confirm congenital defect detected antenatally.
Result: The left kidney has a thin cortical rim and severe hydroureteronephrosis The right kidney has a prominent collecting system, however the APPD has diminished and now measures 0.8cm (previously 1.9cm). No hydroureter is seen. The urinary bladder is empty and heavily trabeculated.
Conclusion: Right kidney improved. Left kidney unchanged.

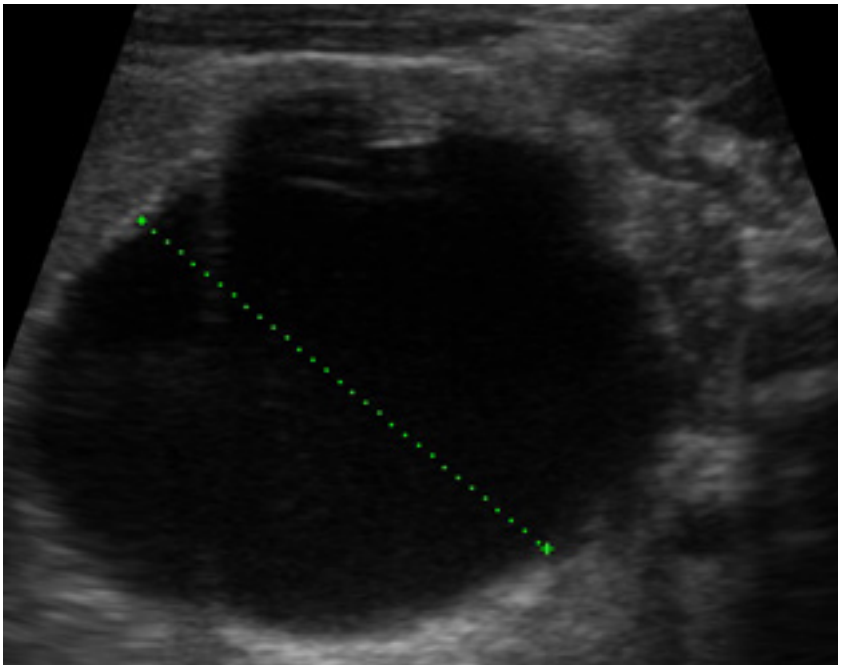

Figure 1: Ultrasound scan showing left hydronephrosis with increased antero-posterior pelvic diameter (APPD).

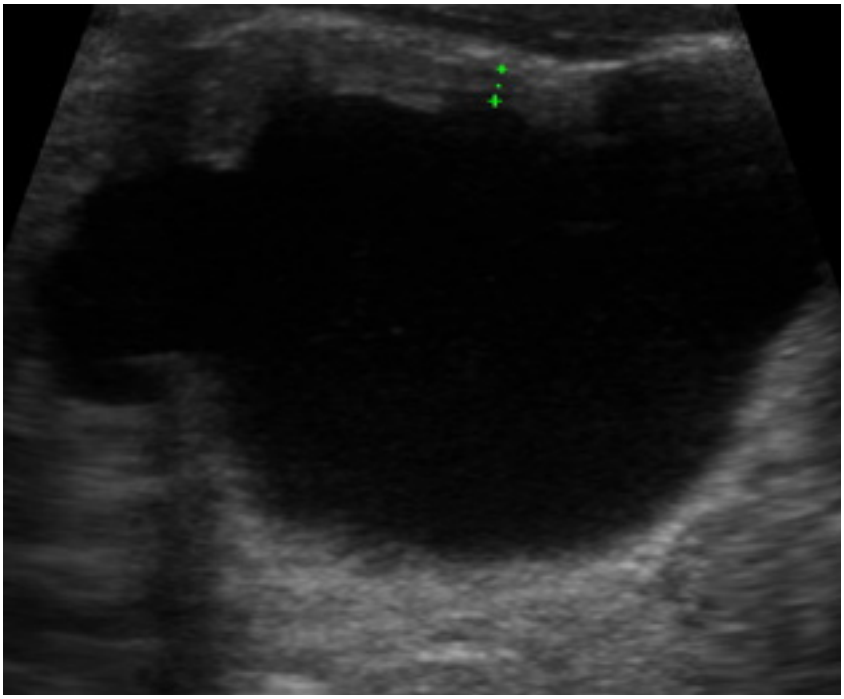

Figure 2: Ultrasound scan showing left hydronephrosis with increased antero-posterior pelvic diameter (APPD).

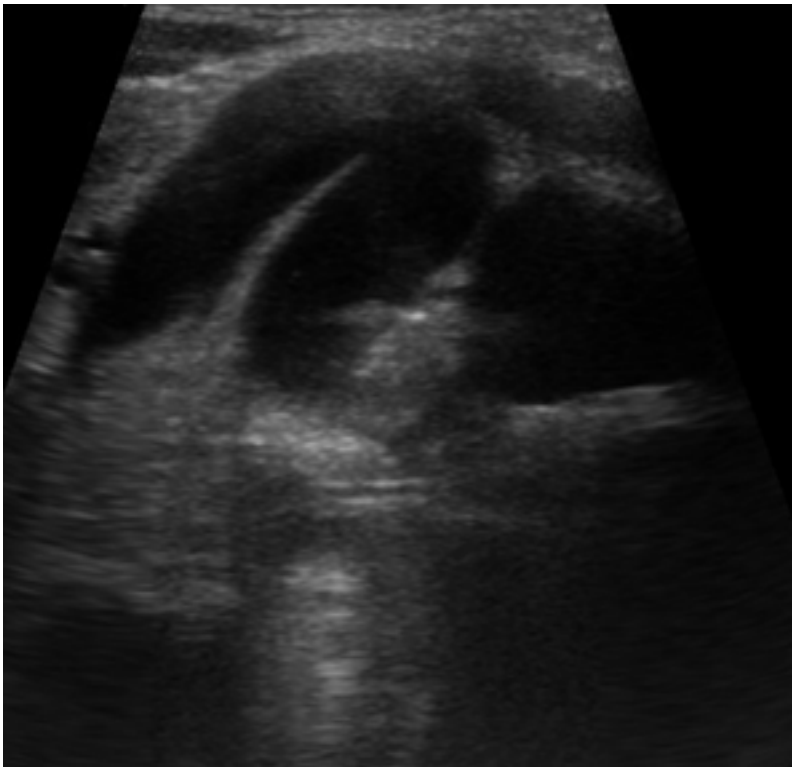

Figure 3: Ultrasound scan showing dilated and tortuous right ureter.

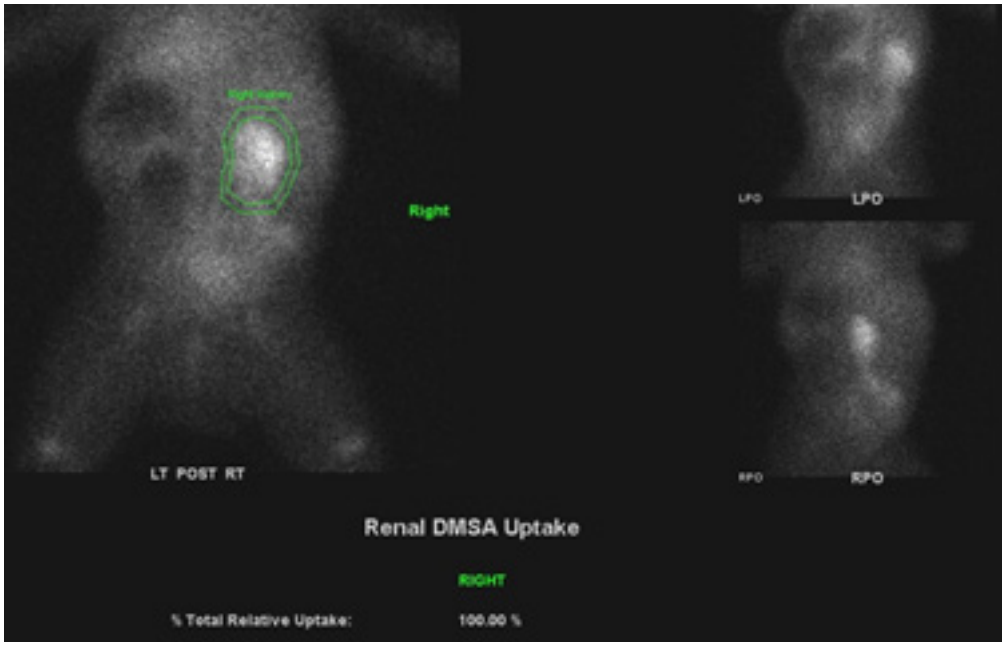

Figure 4: DMSA scan showing single functioning right kidney

Test: Micturating Cystourethrogram
Justification for test: To investigate the anatomy of the bladder and urinary tract, in particular to detect reflux into the upper tracts, exclude posterior urethral valves and bladder wall anomalies.
Result: There is no evidence of active or passive reflux.The urinary bladder is enlarged and elongated. There are no trabeculations or evidence of urachal diverticulii. No evidence of bladder neck hypertrophy is observed. No urethral strictures or urethral irregularities in the region of the external sphincter are present. On micturition the prostatic urethra dilates slightly but there is no evidence of posterior/anterior urethral valves. Incidental note is made of a normal prostatic utricle.
Conclusion: No evidence of posterior urethral valves or reflux. Overall findings are more compatible with prune belly syndrome.

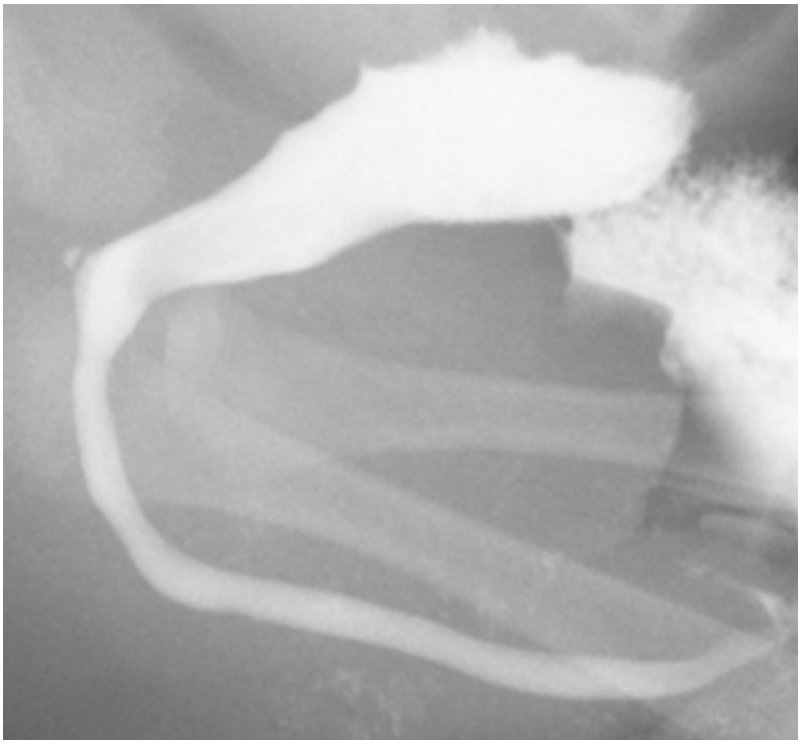

Figure 5: MCUG showing normal posterior urethra

Test: Chest X ray
Justification for test: To look for any abnormalities in the chest.
Result: Bell-shaped chest wall.
Conclusion: Part of the syndrome.

Test: US brain
Justification for test: to look for any associated abnormalities.
Result: Normal.
Conclusion: No associated brain anomaly.

Test: Echocardiogram
Justification for test: to exclude a cardiac anomaly.
Result: Normal.
Conclusion: No associated cardiac anomaly.

Test: NM DTPA Scan
Justification for test: To exclude outflow tract obstruction and get a measure of GFR.
Result: Kidneys in situ. Right kidney of normal size and morphology, with inhomogeneous tracer uptake

in the cortical phase. There is marked stasis in the collecting system with good washout following administration of diuretic. The left kidney shows a minimal amount of functioning tissue and outflow tract and therefore cannot be evaluated.
Conclusion: There is high background activity throughout the study suggestive of renal failure.

Test: US of testes
Justification for test: To assess the testes.
Result: The left testis is located at the superficial inguinal ring, however it could not be advanced further than this and was seen to easily spontaneously reduce back into the inguinal canal. The right testis was not identified in the scrotum or inguinal canal, however an ovoid structure of identical echogenicity located between the right side of the bladder and the distended distal right ureter is felt to represent an intra-abdominal testis.
Conclusion: Both testes are undescended.

Test: US of the spine
Justification for test: To exclude spinal anomalies.
Result: The cord terminates at L2 level. The visualised cord, conus medullaris and cauda equina roots are within normal limits. There is no evidence of tethering of the spinal cord or thickening of filum terminale. There is no evidence of a spinal lipoma.
Conclusion: Examination is within normal limits.

Diagnosis:

A diagnosis of Prune belly syndrome was made based on the following signs found during investigations; hydronephrosis found on ultrasound, bell-shaped chest wall found on chest x-ray and cryptorchidism also found on ultrasound.

Final treatment and follow ups:

The child will be continued on ciprofloxacin orally for three days and his EPO will be increased to twice a week. He will be followed up at the pediatric day care by the nephro-urological team.

Fact Box 3:

Name of Condition: Prune Belly Syndrome

Prune Belly Syndrome also known as Eagle-Barrett syndrome or triad syndrome[3]. It is a collection of birth defects involving:

- Poor development of abdominal musculature[4]. This can lead to a poor cough mechanism which will lead to increased pulmonary secretions. The weak musculature may also lead to constipation due to inability to perform the Valsalva maneuver[3]. This may be due to a partial or complete absence of the abdominal muscles[5].
- Cryptorchidism[4], usually bilateral[5]
- Urinary tract abnormalities[4]. Obstruction or upper urinary tract dilation can occur, with the site varying from the pelviureteral junction to the prostatic membranous urethra[3]. The malformations may include dilatation of ureters, hydroureter, hydronephrosis or vesicoureteral reflux[5].

The cause of prune belly syndrome is unknown and affects mostly males. In utero, the fetus' abdomen swells, usually due to a urinary tract abnormality. This fluid disappears after birth resulting in a wrinkled abdomen. This is made more noticeable by the lack of abdominal musculature[4]. Complications include pulmonary hypoplasia and chronic kidney disease[5]. Oligohydraminos in pregnancy can cause lung problems[4].

The mortality rate associated with this syndrome is 20%. The severity of this syndrome varies from patient to patient. No definitive treatment has yet been established[4]. However early surgery to fix weak abdominal muscles, urinary tract problems and cryptorchidism is recommended. Antibiotics may be given to treat or prevent UTIs[4]. It affects 1 in 30,000-40,000 live births, with 96-97% of all cases being males. Twinning is associated with this syndrome, with 4% of all cases being twin pregnancies. It is also associated with trisomy 18 and 21. There is an increased incidence of tetralogy of Fallot and ventriculoseptal defects[3].

Woodhouse et al. (1982) reviewed 47 cases of prune-belly syndrome. They reported varying degrees of abdominal muscle weakness, leading to 'pseudo-prunes'. However these cases still had urinary tract problems. A similar but rarer condition in girls exists. Although the exact cause is not yet known, a two-step autosomal dominant mutation with sex-linked expressions, partially mimicking X-linkage has been suggested. The syndrome has a broad spectrum and so management is disputed. Prognosis depends on the condition of the kidneys at birth, and so classification is useful for management[6].

Weber et al. (2005) discusses the genetic component in posterior urethral valves/prune-belly syndrome (PUV/PBS). The exact etiology of PUV is not yet understood, however population studies suggest a genetic factor. In fact we see a higher incidence of PUV in populations with elevated background rate consanguinity. In one family that had six children, the parents and the one daughter were normal while the boys were all affected. This suggests that the condition is X-linked recessive. The disease might also be digenic, this might explain the low incidence even in siblings since you need both defective genes in order to explain the phenotype[7].

Risk Factors:

- Male gender
- Young maternal age
- Use of herbal concoctions in pregnancy[8]

Symptoms and signs:

Weak abdominal muscles can cause:

- 'Little Buddha' appearance
- Constipation
- Delay in sitting and walking
- Difficulty coughing

Urinary tract problems can lead to difficulty urinating[4].

Investigations to confirm diagnosis:

Ultrasound during pregnancy may show a swollen bladder or enlarged kidney

After birth:

- Blood tests
- Ultrasound
- Voiding cystourethrogram
- X-ray[4] of the chest

Prevention

There is no known prevention for this condition. In rare cases, surgery during pregnancy can be performed after diagnosing a urinary tract obstruction to help prevent progression to prune belly syndrome[4].

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Case Number 4
Motor Vehicle Accident

Joanna Thompson and Nicole Marie Zerafa
Reviewed by: Mr Jason Zammit

Case summary:

Demographic details:

Ms. SD, female.

Ms. SD is a 38-year-old female from Sliema who presented to Accident and Emergency after being involved in a motor vehicle accident. She was the pillion-rider on a motorcycle when the accident occurred and she suffered extensive wounds particularly to her left lower limb. No pulses were felt in her left leg when the ambulance arrived and a circa 10 cm segment of her tibia was lying external to her body on the road. She underwent four surgeries in less than two weeks to repair her blood supply, fix her tibia and pelvis and to close the wound using a skin graft. Another surgery was also carried out a month later to remove some areas of infection in the left tibia and to have a ring fixator applied.

Presenting complaint:

Motor vehicle accident.

History of presenting complaint:

The patient was involved in a motor vehicle accident on Monday 20th October 2014.
She was the pillion-rider on a motorcycle when the vehicle was involved in a head on collision with a taxi, which was driving in the opposite direction (on the other side of the road). Consequently, she was thrown off the vehicle and ended up lying on the ground in immense pain.

Past medical and surgical history:

Past medical history:

Right ankle fracture in 2010 which required no surgery.

Past surgical history:

Wisdom tooth extraction.

Drug history:

No drug history and no known drug allergies.

Family history:

No significant family history

Social history:

She lives in a flat in Sliema on her own where she has stairs. She had no walking problems prior to the accident. She works with an online gaming company.
She used to smoke socially but stopped a few years ago and she drinks 1 to 2 units of alcohol daily.

Systemic inquiry:

- General Health: Has suffered from migraines since childhood .
- Cardiovascular System: Nil to note.
- Respiratory System: Nil to note.
- Gastrointestinal System: Nil to note.
- Genitourinary System: Nil to note.
- Central Nervous System: Nil to note.
- Musculoskeletal System: Nil to note.
- Endocrine System: Nil to note.
- Others: Nil to note.

Discussion of results of general and specific examinations:

Upon arrival of the ambulance, she was found lying on her right side in a semiconscious state. Her eyes were open and she was occasionally responsive. Her left lower limb showed extensive damage with both soft tissue loss and bone exposure. A piece of her left tibia was found lying on the road outside of her leg. On examination on site, there was no pulse present in her left foot (dorsalis pedis and posterior tibial pulses) and a weak radial pulse was noted, possibly due to shock. Pulses in the right foot were palpable. Blood loss on site was estimated to be around 500mL.

Diagnostic procedures:

The following blood tests were done: Urgent crossmatch, CBC, Urea & Electrolytes & Creatinine, RBG, V/ABGs, APTT/INR.
Doppler ultrasound was used to check the dorsalis pedis and posterior tibial pulses. These were both found to be pulseless in the left lower limb.
An urgent polytrauma CT was carried out.
X-rays were taken throughout management of the injuries, to monitor progress and to guide the surgeries.

Therapy:

She was given ketamine immediately for pain relief and sedation which allowed the left lower limb to be reduced on site with external fixation applied subsequently.
On arrival at the hospital, the wound on her left lower limb was cleaned with saline and dressed. She was given a blood transfusion as well as the following medications:

Drug	Route administered	Use
On arrival: 1. Ketamine 2. Saline 3. Cyklokapron (Tranexamic acid)	All were administered IV	1. An anaesthetic agent to reduce pain 2. To replace fluid loss 3. An antifibrinolytic to reduce bleeding
Ciprofloxacin	IV	An antibiotic – used prophylactically especially since the patient suffered a severe open wound.
Clindamycin	IV	Same reason as above.
Clotiapine	IV	An antipsychotic: used to reduce confusion and delusions.
Succinylcholine	IV	Used during orthopaedic operations as a muscle relaxant.

Surgery 1: 20th October 2014

On the 20th October (from ca. 11.30 pm till around 6.30 am the next day) she was taken for emergency surgery where she was initially operated on by the vascular surgeons in an attempt to restore the blood supply to her left lower leg. This was done by taking a venous graft (the lesser saphenous vein) and using it to create a femoro-popliteal bypass. Heparin IV 3000U was given to reduce the risk of developing deep vein thrombosis after the surgery.

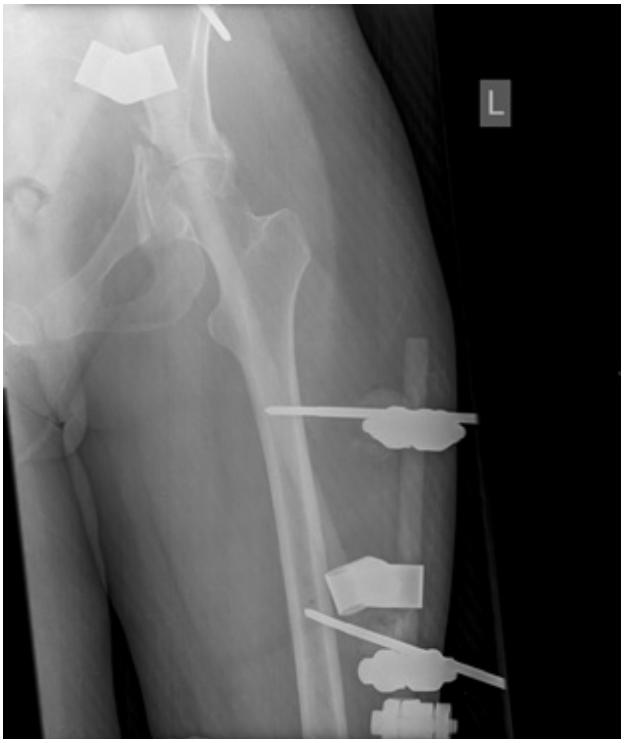


Figure 1: An X-ray showing the acetabular fracture after initial fixing with an external fixator on 21st October

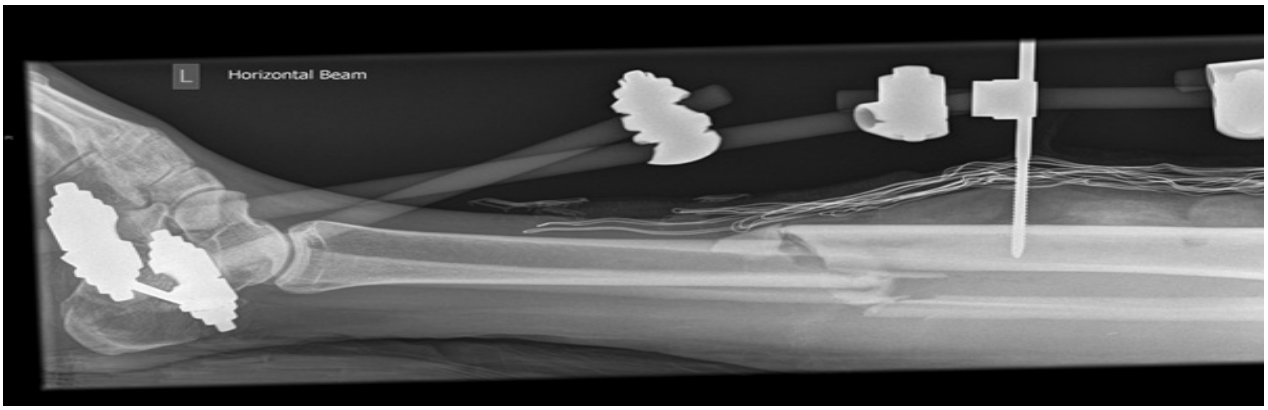


Figure 2: An X-ray taken on 21st October showing the external fixation done during the first surgery.

Once both the dorsalis pedis and tibialis posterior pulses were restored, the orthopaedic surgeons operated on her left lower limb: the tibia that had been found outside of her leg was fixed back in place after thorough cleaning, the fragments of the lateral condyle of the tibia were held in place with a wire and finally the entire left lower limb was fixed using external fixator rods – from her left ankle all the way up to her pelvis.

Following this procedure, she was taken to the Intensive Care Unit for post-operative monitoring. She was then transferred to the orthopaedic ward to await her next surgery. During this time she asked for HIV and Hepatitis B and C blood tests to be carried out.

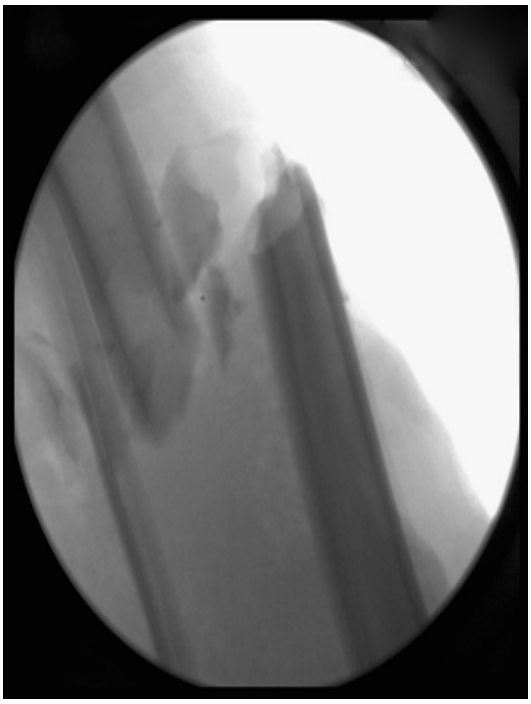


Figure 3: A theatre fluoroscopy of the severely damaged tibia during the first emergency surgery on 21st October.

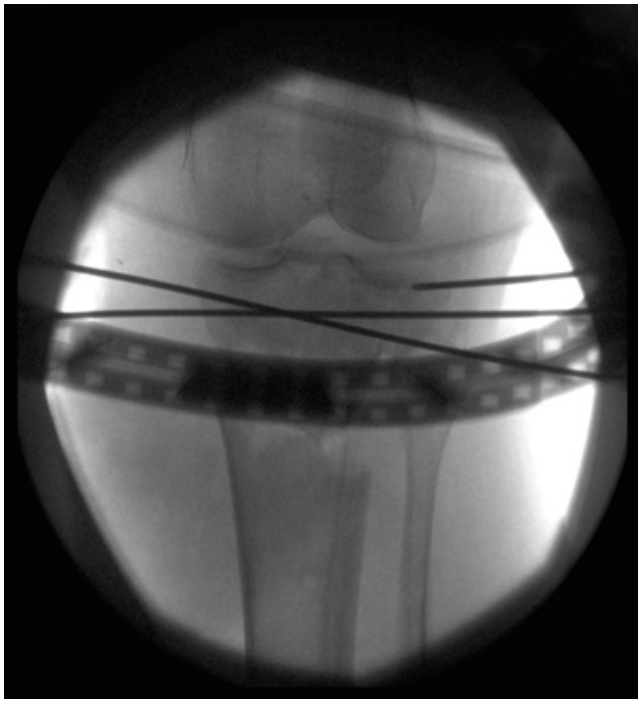


Figure 4: A theatre fluoroscopy of the left knee after wiring and fixation after the surgery on 25th October.

<u>*Surgery 2: 25th October 2014*</u>

During this surgery, the external fixator rods on her leg were replaced with external fixator rings. Her pelvis was fixed in two stages due to it having been broken both posteriorly and anteriorly. During this particular surgery, the pelvis was openly reduced and internally fixed anteriorly using screws.

Finally a partial flap from her left gastrocnemius was placed over the massive wound on her left leg to keep the leg bones beneath vascularised and covered until the plastic surgeons could operate and place a complete flap over the wound in a subsequent surgery.

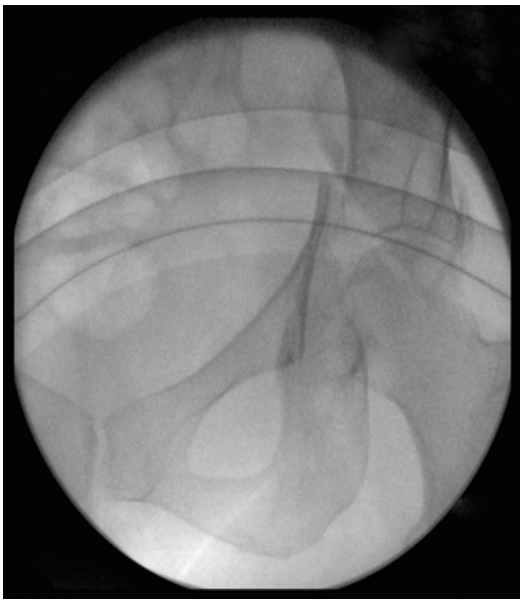


Figure 5: A theatre fluoroscopy of the acetabular after fracture prior to internal fixation on 25th October.

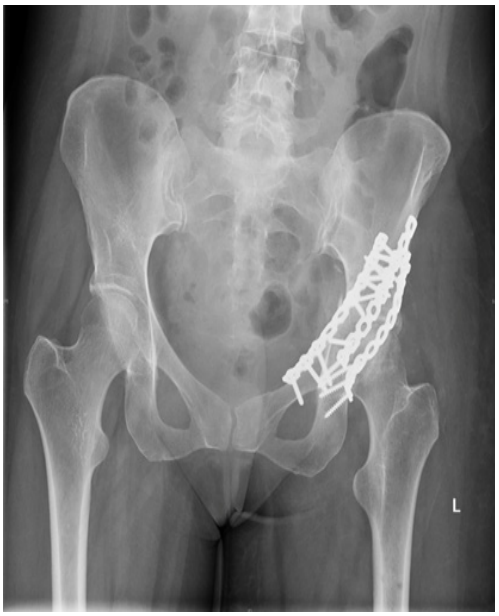


Figure 6: An X-ray taken on 29th October all major surgeries on the pelvis, showing the final internal fixation of the acetabulum.

Surgery 3: 28th October 2014

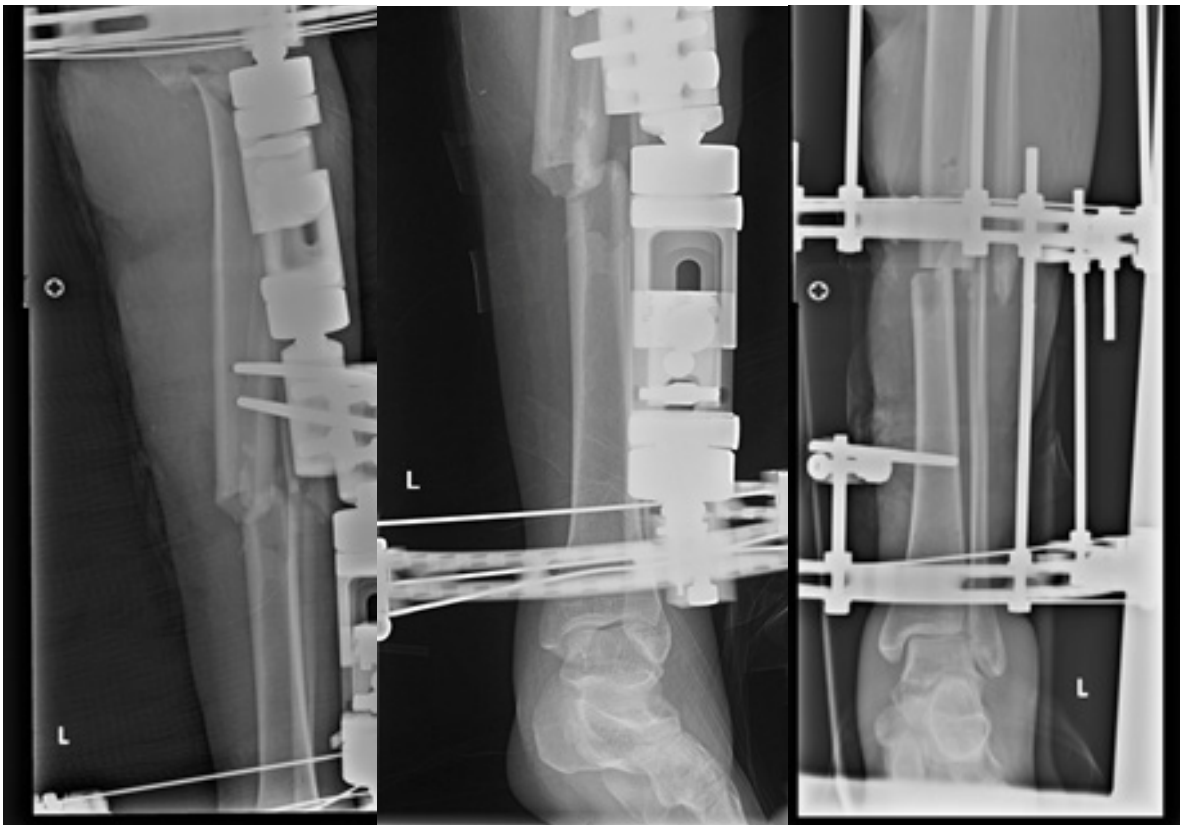
This was the second operation on her pelvis and consisted of an open reduction and internal fixation of the left acetabulum from a posterior approach, as well as a superficial skin grafting of the tibial wound.

Surgery 4: 1st November 2014

This time plastic surgeons were involved in making a fascio-cutaneous flap based laterally on her left lower limb, covering the gastrocnemius.

Surgery 5: 2nd December 2014

This was her final surgery where she had segmental excision of 3cm of infected left tibial fracture, adjustment of a ring fixator and local rotation skin flap for closure.



Figures 7, 8 and 9: Three X-rays which are arranged chronologically from left to right. The first was taken on 13th November, the next on 29th November and the final one on 4th December after her final surgery on 4th December 2014. These show the progress of the tibia from the initial damage, as the alignment improves slowly till a few days before discharge.

The following are the drugs she was given during her stay in hospital:

Surgery 1

Date	Drug	Route	Dose	Frequency	Reason
21/10/14	Morphine	IV	1mg	PRN	Opioid pain medication used to treat moderate to severe pain. Patient controlled anaesthesia.
	Protifar	PO	2 scoops	TDS	A special food for medical use to correct hypoproteinaemia.
	Paracetamol	PO/IV	1g	QDS	An analgesic.
	Metronidazole	IV	500mg	TDS	An antibiotic for anaerobe cover.
	Clindamycin	IV	600mg	TDS	An antibiotic-prophylactic use.
	Ciprofloxacin	IV	400mg	BD	An antibiotic-prophylactic use.
22/10/14	Clexane-low molecular weight heparin	SC	40mg	Daily	An anticoagulant therapy to prevent formation of blood clots post-operatively.
23/10/14	Co-amoxiclav	IV	1.2g	TDS	A penicillin antibiotic.

Surgery 2 and 3

Date	Drug	Route	Dose	Frequency	Reason
28/10/14	Gentamicin	IV	320mg	Daily	An antibiotic-used to treat severe bacterial infections.
	Flucloxallin	IV	2g	QDS	A penicillin antibiotic.
29/10/14	Clexane- low molecular weight heparin	SC	40mg	Daily	An anticoagulant therapy to prevent formation of blood clots post-operatively.
	Diclofenac	PO	50mg	TDS	A non-steroidal anti-inflammatory drug.

Surgery 4

Date	Drug	Route	Dose	Frequency	Reason
1/11/2014	Lactulose	PO	10g	Daily	Medication to treat constipation.
	Protifar	PO	1 sachet	TDS	A special food for medical use to correct hypoproteinaemia.
14/11/2014	Codeine	PO	30mg	TDS	An opioid pain reliever used to treat mild and moderately severe pain.
17/11/2014	Ibuprofen	PO	400mg	TDS	A non-steroidal anti-inflammatory drug.

Surgery 5

Date	Drug	Route	Dose	Frequency	Reason
4/12/2014	Prochlorperazine	IM	12.5mg	Daily	An anti-emetic used to prevent and treat nausea and vomiting.
6/12/2014	Prochlorperazine	PO	5mg	Daily/PRN	An anti-emetic used to prevent and treat nausea and vomiting.
7/12/2014	Hydroxyzine	PO	25mg	Nocte/PRN	A sedative used to treat anxiety and tension, as well as an antihistamine.

All throughout her stay in hospital, she was being seen by a physiotherapist and monitored by the orthopaedic staff.

Final treatment and follow up:

Discharged on 15th November 2014.
Plan on discharge:
-Change dressings every 3 days.
-Orthopaedics outpatient visit on 7th January 2015 – X-ray of the pelvis and left leg should be taken on the day.
-Another orthopaedics outpatient visit on 15th January 2015.

Fact Box 4:

Title: Motor Vehicle Accident

Motor vehicle accidents are commonplace in Malta. During the year of 2013 a total of 14,070 accidents were reported, according to the National Statistics Office of Malta. Of these, only 18 were fatal and 14 of these fatalities were males. It also emerged that no passengers were among these 18 fatalities, but 2 pedestrians were.

At the moment, the European Commission for Mobility and Transport is collecting data from all countries of the EU and studying the trends of traffic accidents and fatalities in a massive Road Safety Programme. The aim of this programme is to reduce the number of fatalities due to traffic accidents by improving a number of factors, including road safety and drivers' behaviour. The total number of deaths in the EU (28 countries) due to traffic accidents in 2012 was 28,100 – 11 of them were in Malta.

For its small size, Malta may only have a small amount of fatalities, but the differences in infrastructure of the country have to be taken into consideration too: while abroad many countries have large motorways and rather high average speeds, Malta has very short, narrow roads which should make drivers drive at much slower average velocities. Hence one might still want to find out why 18 people in 2013 and 11 in 2012 died in Malta due to road traffic accidents when cars are meant to be travelling so slowly: is it poor road safety, or the road users' negligent behaviour?

References:

1. http://nso.gov.mt/en/News_Releases/View_Current_Year/Pages/2014-(1).asp
2. http://ec.europa.eu/transport/road_safety/specialist/statistics/index_en.htm
3. http://ec.europa.eu/transport/road_safety/pdf/observatory/trends_figures.pdf

Case Number 5
Liver Abscesses

Thomas Gatt
Reviewed by: Mr Dennis Gatt. M.R.C.S., L.R.C.P.(Lond.), F.R.C.S.(Eng.) F.R.C.S. (Edin.)

Case Summary:

Demographic details:

Mr. CG, male.
Referred from: GP.

A 69 year-old smoker presented to casualty with a one month history of worsening right upper quadrant pain and lethargy. The patient also complained of constipation and decreased appetite. Initial examination revealed noticeable hepatomegaly while initial blood tests showed a very high white blood cell count coupled with deranged liver function tests. The patient underwent a CT abdomen pelvis, which showed 2 large pyogenic liver abscesses of unknown origin. The patient was started on antibiotics and underwent US guided drainage of the abscesses. The pus was sent to microbiology lab for microscopy, culture and sensitivity. The patient was monitored until the abscesses began to resolve and was investigated further to try and establish the cause of these abscesses. The patient was discharged 21 days post-admission.

Presenting complaint:

Lethargy: 4 weeks
Worsening RUQ abdominal pain: 4 weeks
Decreased appetite
Worsening constipation

History of presenting complaint:

Mr. CG, a 69-year-old male, was referred to A&E, complaining with a one month history of lethargy and worsening abdominal right upper quadrant pain with no radiation. The patient also gave a history of worsening constipation and decreased appetite. He was seen by his GP, who prescribed omeprazole and antibiotics to no effect. The patient had no nausea, no vomiting and no lower urinary tract symptoms, however admitted to occasional night sweats, chills and rigors. No fever was documented.

Past medical and surgical history:

Past medical history:

Previously healthy. Nil of note.

Past surgical history:

Previously healthy. Nil of note.

Drug history:

Drug	Dosage	Frequency	Type	Reason
Omeprazole	20mg	BD	Proton Pump Inhibitor	Relief of RUQ pain
Forceval	1 tablet	Daily	Antacid	Reduces stomach acid

Family history:

Nil to note.

Social history:

Mr. CG is married and lives with his wife. He admits to smoking 2 packets a day since he was young and drinks alcohol socially.

Systemic inquiry:

- General Health: Looks well in general, patient appeared dehydrated
- Cardiovascular System: Lower limb oedema noted
- Respiratory System: Crepitations heard at base of left lung
- Gastrointestinal Tract: Constipated, distended abdomen, tender epigastrium and RUQ pain. 3cm finger breath hepatomegaly was noticed. DRE normal.
- Genitourinary System: Nil of note
- Central Nervous System: Nil of note
- Musculoskeletal System: Nil of note
- Endocrine System: Nil of note

Current Therapy:

Drug	Dosage	Frequency	Type	Reason
Hartmann's solution	1L	8-hourly	Rehydration IV solution	To ensure good hydration
Omeprazole	30mg	BD	Proton pump inhibitor	Inhibits acid production in stomach
Ranitidine	50mg	TDS	Histamine receptor antagonist	Inhibits acid production in stomach
Paracetamol	1g	6 hourly	Analgesic	Pain relief

Discussion of results of general and specific examination:

On general examination, the patient appeared alert, oriented and well. The patient did not appear to be jaundiced, pale or cyanosed. His pulse was measured at 90 beats per min, with an SpO2 of 99% on air and a blood pressure of 135/82. The patient was afebrile, with a body temperature of 37.2°C.

Examinations of the cardiovascular and respiratory systems were unremarkable. A normal respiratory rate of 18/min was observed, together with equal air entry on both sites. Minimal lower limb oedema and crepitations at the base of the left lung were the only features of note.

An abdominal examination revealed a tender and distended abdomen, specifically with right upper

quadrant pain. A 3cm fingerbreadth hepatomegaly was found. The patient had no nausea, diarrhoea or vomiting. A digital rectal exam was found to be normal, as was examination of the hernial orifices.

In view of the examination findings, the patient was initially sent for x-rays of the chest and abdomen.

Differential diagnosis:

- Peptic ulcer disease
- Acute cholecystitis
- Pancreatitis
- Appendicitis
- Musculoskeletal pain
- Intestinal obstruction
- Liver abscess

Diagnostic procedures:

Laboratory Exams:

Test: Blood tests 11/12/14 and 12/12/14
Justification for test: Obtain baseline values and make a diagnosis according to the clinical findings.
Result:
Complete blood count:
White blood cell count: 21.3 x 10^9/l [4-11x10^9/l]
Neutrophils: 19.44 x10^9/l [2-7.5x10^9/l]
Urea and electrolytes: Normal
Creatinine: Normal
Amylase: Normal
Urinalysis: Negative
Liver function tests:
Alkaline Phosphatase: 235U/l [40-129U/l]
Alanine aminotransferase: 43U/l [5-41U/l]
Gamma Glutamyl Transferase: 160U/l [8-61 U/l]

Test: Microbiology Culture & Sensitivity (13/11/14)
Justification for test: Pus was sent to the lab to identify the organisms causing the pathology.
Result: Abundant polymorphs, gram positive cocci in clusters and in chains as well as gram negative rods were found. Eventually a more detailed report identifying cultures of *Klebsiella pneumoniae (K. pneumoniae)* and *Morganella morganii (M. morganii)* was later issued.

Radiological and Instrumental investigations:

Test: Chest Xray (11/11/14)
Justification for test: Basic Investigation and to identify possible pathology.
Result: No abnormality detected.

Test: Abdominal Xray (11/11/14)
Justification for test: Basic Investigation and to identify possible pathology.
Result: Faecal loading and gas.

Test: CT Abdomen and Pelvis (11/11/14)
Justification for test: To identify cause of leucocytosis.
Result: Two non-communicating abscesses located in the liver which containing fluid and gases.

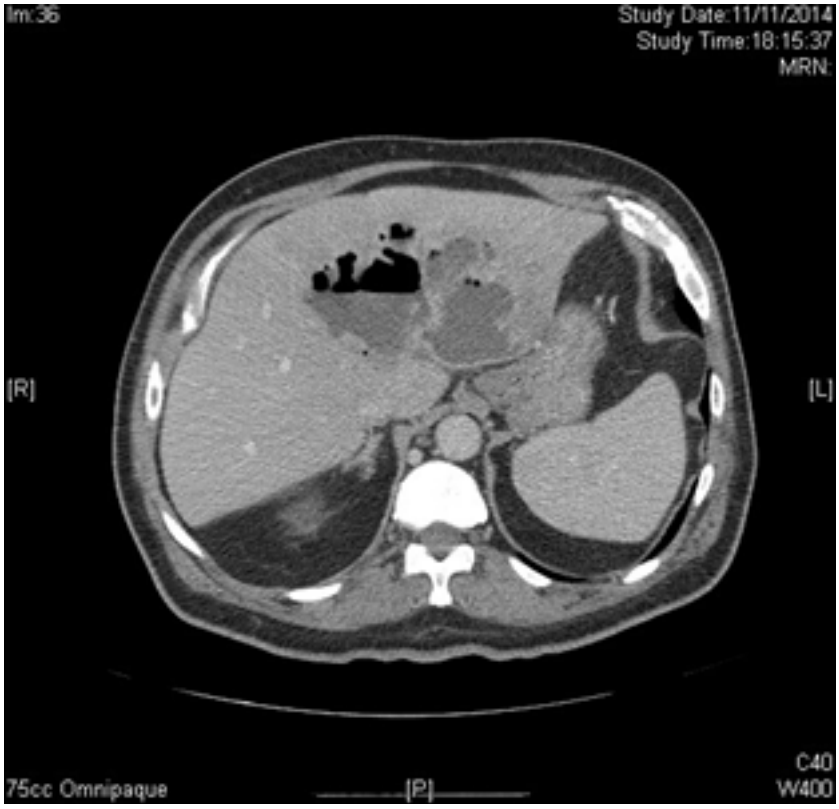


Figure 1: The CT Abdomen Pelvis showing the 2 non-communicating abscesses. Note the irregular shaped margins and the fluid-gas levels present.

Test: Colonoscopy (21/11/14)
Justification for test: To identify any potential sources of infection which could have led to abscesses.
Result: Normal, except for a polyp found at 30cm which was removed.
Conclusion: No potential sources of infection detected.

Test: MRI of Pancreas (still pending at time of writing)
Justification for test: Non-urgent investigation to exclude any biliary strictures.
Results: n/a

Therapy:

Drugs:

Drug Name	Dosage	Frequency	Type	Reason
Enoxaparin	40mg	Daily	Anticoagulant	Thromboprophylaxis in immobile patient (high risk due to smoking)
Tazocin	4.5mg	TDS	Antibiotic	Broad spectrum antibiotic

Metronidazole	500mg	TDS	Antibiotic	Broad spectrum for anaerobic bacteria

Management:

The patient was admitted, his parameters monitored and bloods and urine samples were taken. Initial chest and abdominal x-rays revealed nothing significant. A CT scan was carried out, revealing two liver abscesses. The patient was kept nil by mouth, given 1 litre IV Hartmann's solution 8 hourly and started on a 4.5mg dose of the antibiotic Tazocin, three times daily. The patient's WBC and LFTs were abnormally high as indicated in the section on Laboratory Investigations above.

On day 2 post admission, an ultrasound-guided drainage of the liver abscesses was ordered. The patient was started on a 500mg dose of metronidazole IV, three times daily.

On day 3, the patient was seen to be well and appeared to be responding to the antibiotic therapy. His abdomen was soft and non-tender on examination. Two 12F drains were inserted into the two liver abscesses under ultrasound guidance. The drains were attached to bags and allowed to drain freely, collecting around 230mL of pus. No immediate complications occurred. The pus was sent to the microbiology lab for microscopy, culture and sensitivity (MCS) testing. A direct gram stain report from the microbiology lab showed the pus to contain a mixture of gram positive cocci in clusters and chains, as well as gram negative rods.

On day 5, it was noted that the patient's WBC count had decreased from 16.8 to 14.8. The liver function tests were however still deranged with a high ALP of 191 (normal range; 40-124) and a high GGT of 141 (normal range; 8-61). The two drains in the upper abdomen collected a further 50ml each since last recorded two days previously.

On day 8, the WBC had decreased further to 14.1, however the albumin was found to have risen to 24. A detailed report of MCS from the lab showed the presence of Klebsiella pneumoniae and Morganella morganii. A colonoscopy was scheduled to exclude any colonic sources of infection which may have given rise to the liver abscesses. The case was also discussed with a consultant gastroenterologist who suggested an MR of the pancreas to exclude any biliary strictures.

The patient took bowel preparation over the next 3 days until a colonoscopy could be performed. No abnormalities were detected except for a polyp which was removed. In the meantime, the abscesses appeared to be draining well and the patient was stable. His albumin levels were increasing once again. On further questioning, the patient admitted to having had a chest infection a couple of weeks prior to admission. A follow up US was carried out to observe the resolving abscesses.

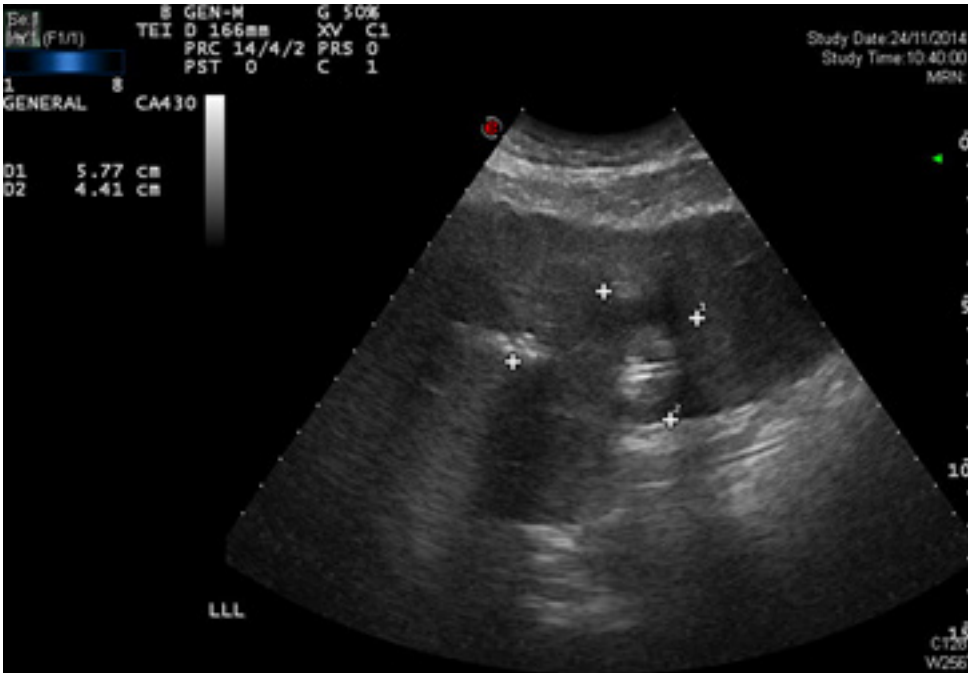


Figure 2: A follow up US scan showing the abscesses draining well and beginning to resolve.

The patient was kept in hospital until his liver function tests improved, his albumin levels increased, his CRP went down and his WCC returned to normal. Prior to discharge, the patient was discussed with microbiologists who advised levofloxacin (Tavanic) for the next 5 days and then to stop treatment. The patient was discharged 21 days post admission, with the drains intact, and scheduled to return 10 days later for drain removal and review.

Diagnosis:

There are 3 major types of liver abscesses which can be classified according to the underlying aetiology;

- Pyogenic liver abscesses, which are commonest in the Western world and are typically polymicrobial.
- Amoebic abscesses, which are more common in the developing world, the major causative organism being *Entamoeba histolytica*.
- Fungal abscesses, which generally account for fewer than 10% of cases and are typically due to *Candida* species[1-2].

In this patient, the cause of the liver abscess is seemingly cryptogenic. In normal cases, liver abscesses typically occur due to an infection in the abdominal cavity (e.g. following appendicitis or diverticulitis). Other potential causes include biliary tract infection (e.g. ascending cholangitis), septicaemia and liver trauma[3].

A prominent feature in this case is the lack of severity of symptoms the patient presented with, especially when considering the size of the abscesses formed. In 95% of cases, the patient typically presents with a high grade fever[4] which was absent in this case. Other typical symptoms of jaundice, nausea and vomiting were also absent.

K. pneumoniae, one of the pathogens found inside the abscesses of this patient, is known to be commonly associated with liver abscesses. In fact, over the past two decades *K. pneumoniae* has surpassed Escherichia coli as the prominent bacteria found in such pyogenic liver abcesses[3]. While its predominance is found to be increasing worldwide, an extraordinary significant number of cases have been documented in Taiwan[4]. Recent studies by Chen, S.C. et al which sought to compare *E.coli* and *K. pneumoniae* liver abscesses

concluded that in the case of *K. pneumoniae*, the cause is typically cryptogenic[4], as appears to be the case in this patient. However *K. pneumoniae* abscesses are also typically associated with diabetes mellitus[4] which was not the case in this particular patient.

K. pneumoniae is associated with pneumonia and other chest infections such as bronchitis or bronchopneumonia. If the patient's claim of a chest infection prior to admission is correct, this may explain the presence of the organism in his body which would have reached the liver by haematogenous spread.

The presence of *M. morganii* in the pus specimen cultured is also noteworthy. While typically a commensal gram negative bacteria found in the intestine, cases have also been documented of this pathogen in cases of pneumonia, as well as bacteraemia. Mucosal defects of the colon may provide a route for invasion of bacteria into the portal system, and subsequent spread to the liver via the blood. In a colonoscopy, performed on the patient on day 11 post-admission, no evident signs of pathology were found and it was concluded that the presence of the M. morganii in the abscess was unlikely to have originated from the colon.

In a study carried out by Jeong et al on 230 patients with pyogenic liver abscesses, they showed evidence that cryptogenic liver abscesses may actually herald colonic cancers, especially in patients with *K. pneumoniae* abscesses and diabetes mellitus. In cases were colonoscopy was indicated as a means of investigation, typical findings included carcinoma, polyps and diverticula in over 80% of cryptogenic cases[6].

Prognosis is generally positive if treated by drainage and with the correct antibiotics. In a 6-year study of 248 pyogenic liver abscesses, the mortality rate of *K. pneumoniae* was found to be only 4.1% when compared to the non-*K. pneumoniae* group which had a rate of 20.8%. No significant differences in relapse were recorded (6.4%)[7].

What makes this case peculiar is the uncharacteristic way in which the patient presented to hospital. It is difficult to deduce the exact cause of the abscesses, since it is hard to distinguish between a bacteraemia caused by a preceding infection or a primary cryptogenic abscess; both of which have been recorded in the past.

Final Treatment and Follow ups:

Following the US guided drainage of the liver abscess, the patient began to make an immediate recovery. He was discharged 21 days post-admission, with the drains intact and started on levofloxacin, 500mg daily for 6 days. After 10 days, he returned for drain removal. On review, his condition seems to have resolved completely.

Fact Box 5:

Sri Vidya Sundara

Title: Liver Abscesses

The three main forms of abscesses, as classified by aetiology are[1]:
1. Pyogenic abscess – often polymicrobial and the global incidence can be variable between 3-25 per 10,000 paediatric admissions.
2. Amoebic liver abscess - attributable to 10% of cases and is due to Entamoeba histoloytica accounts for 10%.
3. Fungal abscess – accounts for less than 10% of cases and is frequently due to Candida.

Pyogenic liver abscess (PLA) has been reported since the time of Hippocrates and account for almost 80% of all cases. Peak incidence is towards sixth and seventh decades of life and typically associated with underlying disease.[2]

Signs and Symptoms[3]*:*

- Fever
- Right upper quadrant pain
- Chills
- Nausea
- Vomiting
- Weight loss
- Jaundice

Causes of PLA[4]*:*

- Diseases of biliary tract
- Infectious gastrointestinal disorders spreading via the portal vein
- Haemotogeneous spread via the hepatic artery
- Direct extension from an intra-abdominal infection
- Trauma

Investigations[1]*:*

- Ultrasonography
- Computer tomography
- Liver function tests

Treatment and prognosis[2,5]*:*

- Small abscesses:

-Systemic antimicrobial therapy
-Broad spectrum antibiotics (administered parentally)

- Large uniloculated abscess

-Percutaneous drainage plus antibiotics

- Large multiloculated abscess

-Surgical therapy

In the last 25 years, mortality rates have decreased from 9-80% to 5-30%[6].

References:

1. Chen S, Huang C, Tsai S, Yen C, Lin D, Wang P, et al. Severity of disease as main predictor for mortality in patients with pyogenic liver abscess. The American Journal of Surgery 2015/04;198(2):164-172.
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5. Hope W, Vrochides D, Newcomb W, Mayo-Smith W, Iannitti D. Optimal treatment of hepatic abscesses. Am Surg 2008;74(2):178-82.
6. Rahimian J, Wilson T, Oram V, Holzman RS. Pyogenic Liver Abscess: Recent Trends in Etiology and Mortality. Clinical Infectious Diseases 2004 December 01;39(11):1654-1659.

Case Number 6
Mucinous Cystadenocarcinoma of the Appendix

Elena Farrugia and Maria Grazia Grech
Reviewed by: Mr. Dennis T. Gatt L.R.C.P. (Lond.), F.R.C.S. (Eng.), F.R.C.S. (Edin.)

Case summary:

Demographic details:
Ms. GM, female, 67 years.
Referred from hospital.

GM, a 67-year-old female, was referred after an appendiceal mucocoele which had been noted and removed during a total abdominal hysterectomy with bilateral oophorectomy (TAH-BSO) was diagnosed on histopathology as being a mucinous cystadenocarcinoma. The patient presented with no signs or symptoms. The patient subsequently underwent a laparoscopic right hemicolectomy and is being followed up at surgical outpatients yearly to exclude recurrence of the malignancy.

Presenting complaint:

The patient was admitted for laparoscopic right hemicolectomy after an appendiceal mass removed during a TAH-BSO procedure was diagnosed as being a mucinous cystadenocarcinoma on histopathology.

History of presenting complaint:

The patient had been admitted for a TAH-BSO procedure after a 7 x 7.8cm complex mass was seen on ultrasound in the right adnexa, which was subsequently confirmed on CT scan as being a cystic mass arising from the right ovary. During surgery however, while the ovaries and the uterus looked normal, a large appendiceal mucocoele was noted and removed via appendectomy. This was then sent to histology where it was diagnosed as being mucinous cystadenocarcinoma.

Past medical and surgical history:

Past medical history:

Depression

Past drug history

Total abdominal hysterectomy with bilateral salpingo-oophorectomy on 6/4/2010

Drug history:

Drug Name	Dosage	Route	Frequency	Reason
Paroxetine	20mg	PO	BD	Anti-depressant
Flupentixol	0.5mg	PO	BD	Anti-psychotic
Lorazepam	1mg	PO	BD	Anti-anxiety

No known drug allergies or anaesthetic problems.

Family history:

No relevant family history.

Social history:

The patient lives with her daughter. She is now retired and used to work as a cleaner. The patient is a non-smoker and does not drink alcohol.

Systemic inquiry:

- General Health: Good and active. Patient looked comfortable after operation
- Cardiovascular System: Nil to note
- Respiratory System: Nil to note
- Gastrointestinal System: Some tenderness close to the operation site for the TAH-BSO procedure
- Genitourinary System: Nil to note
- Central Nervous System: Nil to note
- Musculoskeletal System: Nil to note
- Endocrine System: Nil to note

Discussion of results of general and specific examinations

General examination of the patient was unremarkable. The patient appeared healthy, with no physical signs and symptoms of mucinous cystadenocarcinoma. The patient was not pale, jaundiced or cyanosed. There were no evident signs of recent weight loss and the patient denied recent rapid weight loss. She was afebrile.

Cardiovascular and respiratory examinations were also unremarkable. These revealed normal heart sounds S1+S2+0, with equal air entry in both lungs and normal vesicular breath sounds. A Pfannenstiel incision was observed on the abdomen due to the TAH-BSO. The abdominal examination did not reveal any masses or organomegaly. There was no guarding or rebound tenderness. There was some slight suprapubic tenderness close to the TAH-BSO operation site. Normal bowel sounds were auscultated and stools were normal.

Differential diagnosis:

- Mucinous cystadenocarcinoma
- Carcinoid tumour of the appendix
- Mucosal hyperplasia
- Adjacent caecal tumour
- Inspissated mucous causing obstruction
- Appendiceal mucinous cystadenoma
- Appendiceal mucinous adenoma
- Appendiceal adenoma
- Appendiceal ganglioneuroma
- Appendiceal paraganglioma
- Appendiceal lymphoma
- Appendiceal mucinous adenocarcinoma
- Appendiceal adenocarcinoma

Diagnostic procedures:

Laboratory exams:

Test: Appendix specimen taken during TAH-BSO surgery for histology.
Justification for test: Appendiceal mucocoele noted and removed during surgery.
Results: The specimen was that of a previously opened appendix measuring 110 x 55 x 17mm. Examination of its mucosal surface showed numerous papillary projections into the lumen and extensive mucoid clots. Also submitted was a yellowish, mucoid mass measuring 180 x 100 x 15mm.
On microscopy, sections from appendix showed malignant cells with vesicular nuclei and prominent nucleoli and frequent mitotic figures invading the full thickness of the appendiceal wall with a desmoplastic stromal reaction.
Conclusion: Mucinous cystadenocarcinoma was diagnosed.

Test: Colon and ileum removed during right hemicolectomy for pathology.
Justification of test: To confirm that there was no residual malignancy and for adequate clearance of the drainage lymph nodes.
Results: Terminal ileum measuring 48mm in length as well as attached colon measuring 160mm were submitted. Obviously no appendix was present. On opening, no mass was present.
On microscopy, both the ileal and colonic resection margins were free of tumour. There was no residual tumour although there were a number of diverticula present.
Conclusion: No residual malignancy was present.

Therapy:

Surgical therapy:

Pre-operative: The patient had been advised to take Dulcolax 5mg two days prior to admission as well as another 5mg a day before admission. The patient was admitted to the surgical wards from admission lounge a day before the surgery for bowel preparation. Two sachets of Klean-Prep were given. A chest X-Ray and an ECG were carried out. Blood tests were taken and cross-match was carried out for two units of blood. Stool charting was done. Informed consent was obtained.

Operation: Laparoscopic right hemicolectomy.
Insufflation was used at 12mmHg. 4 ports were used. Dense adhesions from the previous surgery were noted. Routine lateral to medial right hemicolectomy was carried out. Specimens were obtained in a bag for histology. The ileal and the colonic margins were anastomosed together via a GIA stapler.

A drain to remove blood or potential anastomotic leakage, a nasogastric tube for gastric decompression and a urinary catheter were inserted.

Post-operative: The patient removed the nasogastric tube a day after surgery. The urinary catheter was removed two days after surgery. The patient passed flatus two days after surgery and opened bowels three days after surgery. The drain was removed four days after surgery. The patient was kept nil by mouth for five days after surgery.

The post-operative medications were as follows:

Drugs:

Drug	Dosage	Route	Frequency	Reason
Paracetamol	1g	PO	6hrly / PRN	Pain relief
Cefuroxime (Zinacef)	750mg	PO	BD	Prophylactic broad-spectrum antibiotic
Metronidazole (Flagyl)	400mg	PO	TDS	Prophylaxis against anaerobic organisms and protozoa
Minihep	5000 IU	SC	Daily	Prophylactic anticoagulant to prevent thromboembolism
Metoclopramide (Maxolon)	10mg	IV	6hrly/PRN	To control nausea and vomiting post-operatively
Pethidine	75mg	IM	PRN	Pain relief
Paroxetine	20mg	PO	BD	Anti-depressant
Flupentixol	0.5mg	PO	BD	Anti-psychotic
Lorazepam	1mg	PO	BD	Anti-anxiety

Diagnosis:

The diagnosis was made by histological examination of the appendix and the mucocoele removed during the TAH-BSO. Mucinous cystadenocarcinoma is a low grade malignancy [1] and one type of appendicular mucocoele. The other types, in order of increasing severity, are: retention cyst, mucosal hyperplasia and mucinous cystadenoma. Mucinous cystadenocarcinoma is however the most severe form of them all.

This classification[2], created by the World Health Organization[3], is based primarily on epithelial structure. Neoplastic epithelium and a severe distention of the appendicular lumen are required to diagnose mucinous cystadenocarcinoma histologically[2]. There is also invasion of the glandular stroma, desmoplastic reaction and presence of epithelial cells in peritoneal implants[4]. The massive growth of the appendix lumen is caused by these cancer cells producing vast amounts of mucin and these cells may spread within the peritoneum causing pseudomyxoma peritonei[1]. In fact, the latter syndrome is found in 50% of cases[5] and involves mucinous ascites and is more informally known as "jelly belly"[4]. The appendicular mucocoeles make up only 0.2-0.4% of appendectomy surgical specimens and mucinous cystadenoma forms 11-20% of these cases[2]. It also forms less than 0.5% of intestinal tumours[5]. Therefore, this condition is quite rare[2]. Patients who develop mucinous cystadenocarcinoma are usually younger than patients with adenocarcinoma of the appendix[4].

It is difficult to ascertain a mucocoele's presence preoperatively even if a meticulous physical examination is carried out[4]. Most mucocoeles are asymptomatic so are only found incidentally. However, when symptoms are present they depend on how complicated the disease is. There is a range of symptoms and signs from a palpable mass in slim patients, right lower quadrant pain, signs of intussusception and bowel obstruction including colicky pain, gastrointestinal bleeding and therefore anaemia to acute abdomen with sepsis[3].

Carcinoembryonic antigen may be elevated[5]. Conventional imaging techniques make it difficult to distinguish mucinous cystadenocarcinoma from adenoma. However, ultrasound and computed tomography (CT) scan are effective at detecting mucocoeles[6]. CT scan is the best imaging modality for preoperative planning of tumour resection as it has an overall sensitivity of 93% for detection of mucocoele rupture, peritoneal mucinous carcinomatosis or pseudomyxoma peritonei and wall calcification[5]. Furthermore,

contrast enhanced ultrasonography was used along with CT scan and ultrasound to pre-operatively diagnose mucinous cystadenocarcinoma[6]. Generally, endoscopy cannot access the appendix for investigation however it may detect other tumours growing simultaneously with the mucinous cystadenocarcinoma in the colon of 13% of patients with mucocoeles. Even though sometimes the mucosal biopsies taken are normal, colonoscopy is useful in distinguishing benign from malignant lesions[3]. Examination of frozen sections taken during surgery and histopathological examination of the specimen after surgery can be carried out for diagnosis[5].

Removing the tumour early may cure the patient. An acceptable form of definitive therapy is right hemicolectomy[5, 1] and is preferable to appendectomy alone as its 10-year survival rate is 65% while that after appendectomy is 37%. However, if there is no pre-operative evidence of other tumours and no evidence at surgery of the tumour having spread to the peritoneum (the peritoneum surrounding not just the appendix but also of the liver and pelvis must be checked for tumour deposits and/or mucus and if these are present samples are taken for histopathological and cytological examination) or invaded the lymph nodes, appendectomy is sufficient to treat the mucocoele.

One surgical treatment suggested, based on the fact that usually mucinous appendicular tumours spread through the wall and rarely to the lymph nodes, is resection of the tumour along with retrocaecal appendiceal lymph nodes and these are sent for frozen section. If these sections are negative appendectomy only is enough. This is not the case if the lymph nodes are positive in that case right hemicolectomy is performed. Open surgery to remove the appendix is preferable to laparoscopy as it lessens the chance of perforation and hence pseudomyxoma peritonei however, if the surgeon sees that the chance of perforation is not that high laparoscopy may be done. If the tumour disseminated, then along with right hemicolectomy, aggressive debulking; oophorectomy and omentectomy are beneficial. Bowel obstruction and/or fistulation often occur so the patient would need to undergo repeated operations. Radiotherapy and chemotherapy are not effective in disseminated disease. Mucinous cystadenocarcinoma tumours grow slower than appendiceal adenocarcinomas which means they have a better prognosis[5].

Prognosis in the long term is affected adversely by perforation of the tumour and leakage of mucus into the peritoneal cavity. In fact, patients with spread beyond the appendix only have a 45% survival after 5 years as compared with 100% survival after 5 years in patients with low grade mucinous tumours confined to the appendix. No follow up is needed in the latter cases[3].

Final treatment and follow ups:

The patient was discharged ten days after surgery. The patient was seen 6 weeks later in surgical outpatients. The patient will be followed up yearly at surgical outpatients to exclude recurrence of malignancy. The patient has already survived for four years since the surgery.

Fact Box 6:

Title: Mucinous Cystadenocarcinoma

Mucinous cystadenocarcinoma is the fourth type of appendicular mucocoele in a grouping system chiefly based on the structure of the epithelium. This forms 11-20% of appendicular mucocoeles. The epithelium is neoplastic[1]; desmoplastic reaction and glandular stromal invasion are present and (but not necessarily) epithelial cells can be found in the peritoneal implants[2]. The lumen of the appendix is also severely distended[1]. This may result in rupture which results in mucinous dissemination into the peritoneum which causes mucinous ascites that is named pseudomyxoma peritonei. This syndrome is more informally known as "jelly belly". There is also a high chance of metastasis to the liver and lymph nodes. Patients suffering from this condition have a poor prognosis[2].

Risk factors:

Females of middle and older age are mostly affected by appendicular mucocoeles therefore of mucinous cystadenocarcinoma[6]. Kalmon and Winningingham[7] identified three factors which may lead to mucocoele formation in the appendix: aseptic content, continuous mucus production and narrowing of the valvular opening of the appendix. Obstruction of the appendix may be caused by bending, torsion, inflammation and ileocaecal tumour[6].

Signs and Symptoms:[2]

How the patient presents depends on whether the mucocoele ruptures or not. If it does not rupture, the majority of patients are asymptomatic and it is difficult to ascertain the mucocoele's presence preoperatively even if a meticulous physical examination is done[2]. That is, the symptoms are non-specific. However, some patients may suffer from pain or even just discomfort and have a palpable mass in the right lower quadrant[3]. The condition is an incidental finding during or after an operation via histological testing[2].

Investigations and diagnosis: [2]

Conventional imaging techniques make it difficult to distinguish mucinous cystadenocarcinoma from adenoma. Furthermore, surgery immediately ensues after diagnosis so as to avoid rupture. However, ultrasound and computed tomography scan are effective at detecting mucocoeles[3].

Prevention:

Treatment depends on the extent of the condition. Ileocaecal resection is performed[3].Sodium oxybate for nighttime use.

Prognosis:

Prognosis in the long term is affected adversely by perforation of the tumour and leakage of mucus into the peritoneal cavity. In fact, patients with spread beyond the appendix only have a 45% survival after 5 years as compared with 100% survival after 5 years in patients with low grade mucinous tumours confined to the appendix[4].

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Case Number 7
Beta thalassemia major with pulmonary hypertension

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Reviewed by: Dr. Daniel Micallef

Case summary:

Demographic details:

Mr. IB, 29
Referred to: A&E

Mr. IB, a 29-year-old gentleman, who is a known case of beta thalassemia major, was referred from the emergency department following an episode of lethargy, cough, exertional dyspnoea and dyspepsia. During his stay, a number of investigations were carried out and the patient was diagnosed with pulmonary hypertension with a mean pulmonary artery pressure of 90-100mmHg – a complication of beta thalassemia.

This is the only reported case in Malta.

Following the diagnosis, the patient was given a number of drugs (see below) to control his symptoms.

Presenting complaint:

Dyspepsia
Exertional dyspnoea
Cough
Lethargy

History of presenting complaint:

The patient was admitted with a presenting complaint of dyspnoea on exertion, lethargy and cough together with dyspepsia. There was no documented history of fever or recent travel.

Past medical history:

Patient was known to suffer from thalassemia major and underwent splenectomy 20 years ago and as a result, the patient is chronically jaundiced. Has a history of blood transfusions as part of treatment for the symptoms of beta thalassemia major.
Beta thalassemia major with iron overload (markedly increased serum ferritin).
Decreased levels of testosterone in setting of low levels of LH and FSH (hypogoandotrophic hypogonadism), a direct effect of iron overload which deposits in the pituitary gland. Bilateral testicular biopsy had shown a reduced number of germinal cells, with an increased number of Sertoli cells. An MRI of pituitary showed rather small pituitary gland, poor enhancement but no lesions and a central pituitary stalk.
Hepatomegaly was confirmed by ultrasound, in which the liver had a hyperechoic homogeneous structure.

Past surgical history

Splenectomy during childhood.

Drug history:

Drug Name	Dosage	Frequency	Type	Reason
Deferasirox (Exjade)	1750mg	Daily	Tablet for oral suspension	Iron chelator to reduce further iron overload
Phenoxymethylpenicillin (Penicillin V)	250mg	QDS	Oral tablet	To prevent infection following splenectomy
Folic acid	5mg	Daily	Oral tablet	For maintenance of normal erythropoiesis, as erythropoiesis increases due to underlying beta thalassemia major

The patient has no known drug allergies (NKDA).

Family history:

The patient has a family history of beta thalassemia. Both parents are known to be carriers of the condition. His sister was also affected and died of the condition.

Social history:

The patient is married and currently unemployed. He tends to binge drink on weekends and smokes a packet of cigarettes a day.

Systemic inquiry:

- General Health: Chronic jaundice and lethargy
- Cardiovascular System: Concentric left ventricular hypertrophy, inferior vena cava dilated, dilated right chambers
- Respiratory System: High raised pulmonary arterial pressure, around 90-100mmHg. Right Ventricular Outflow Tract (RVOT) and Main Pulmonary Artery (MPA) dilated. Exertional dyspnoea, cough.
- Gastrointestinal Tract: Indigestion, dyspepsia
- Genitourinary System: Nil to note
- Central Nervous System: Nil to note
- Musculoskeletal System: Nil to note
- Endocrine System: Iron overload

Discussion of results of general and specific examinations:

On admission to A&E:
Following admission, the following examinations were performed:

Exam	Result
Pulse	110bpm
SpO2	100% on oxygen
Blood pressure	125/76 mmHg
Temperature	Afebrile
CVS sounds	S1 + S2 + 0, raised jugular venous pressure (JVP)
Chest	Clear
Abdomen	Soft and non-tender
ECG	T wave inversion across the anterior leads which was previously present
Chest X-Ray	Cardiomegaly, which was not present on previous chest X-Rays, pericardial effusion with pleural effusion.
Arterial Blood Gases (ABG)	•pO2: 47.9 mmHg •pCO2: 34.6 mmHg
Blood analysis	•Troponin normal •Positive D-dimer levels •Low fibrinogen levels •Lactate: 4.6 •WBC count 140.70x109/L
CT Pulmonary Angiogram (CTPA)	CTPA showed cardiomegaly but excluded pulmonary embolism.

Further specific tests following ward admission:

Exam	Result
Plethysomgraphy	Performed prior to starting treatment for pulmonary hypertension

Chest X-ray revealed a pericardial effusion with pleural effusion. Further examination confirmed free fluid in the abdomen and pelvis together with a few stones in the gall bladder but a normal common bile duct (CBD). Right heart studies were also performed by catheterisation.
Patient also showed persistently increased INR and deranged liver enzymes.

Differential diagnosis:

- Acute haemolytic state, probably secondary to infection, possibly with Disseminated Intravascular Coagulation (DIC).
- Dyspnoea on admission:
    a. Pulmonary embolism – excluded via CTPA.
    b. Chest infection – which was also supported by the high WBC count.
    c. Pulmonary hypertension which was confirmed on investigation.
- Spontaneous increase in INR – probably due to liver dysfunction and possibly DIC secondary to infection.

Diagnostic procedures:

Laboratory Exams:

Test: Arterial Blood Gases (ABG)
Justification for test: To measure the partial pressures of Oxygen (pO2) and Carbon Dioxide (pCO2).
Result: pO2 was 49.7mmHg (75-100mmHg), pCO2 was 34.6mmHg (35-45mmHg)
Conclusion: Low pO2 levels and hence hypoxemia.

Test: Troponin
Justification for test: Troponin used as a marker of heart tissue damage. Beta-thalassemia associated with increased risk of heart tissue damage and cardiovascular diseases.
Result: Normal troponin levels.
Conclusion: Myocardial infarction is excluded.

Test: D-dimer (Fibrin degradation fragment)
Justification for test: Suspected pulmonary embolism; to rule out the presence of a thrombus. Also due to suspected DIC.
Result: Positive D-dimer levels indicative of high levels of fibrin degradation products.
Conclusion: Positive D-dimer levels correspond to possible pulmonary embolism and DIC.

Test: Fibrinogen (Factor I)
Justification for test: Complimentary test to D-Dimer to help with diagnosis of DIC. Test for fibrinogen activity.
Result: Low fibrinogen levels.
Conclusion: Low fibrinogen levels suggestive of increased fibrinogen consumption. Possible DIC.

Instrumental Exam:

Test: Chest X-Ray (CXR)
Justification for test: To identify consolidation, pneumothorax or signs of heart failure.
Result: CXR showed cardiomegaly that was not present on previous CXRs.
Conclusion: Cardiomegaly and query of pericardial effusion.

Test: CT Pulmonary Angiogram (CTPA)
Justification for test: To produce an image of the pulmonary arterial supply using computed tomography and intravenous contrast medium.
Result: CTPA confirmed cardiomegaly but did not show signs of pulmonary embolism.
Conclusion: Pulmonary embolism excluded.

Test: Right Heart Studies/Catheterisation
Justification for test: To determine and assess the function of the heart and the pulmonary arterial pressure.
Result: Right heart studies showed an elevated pulmonary arterial pressure of 90-100mmHg.
Conclusion: Confirmed pulmonary hypertension.

Therapy:

Drugs:

The patient was transfused two units of packed red blood cells (PRC) in view of a low level of haemoglobin (Hb) of 6.6 g/L (13-18 g/L).

Drug	Dosage	Frequency	Formulation	Reason
Meropenem	1mg	Every 8 hours	Infusion	To treat possible infection in lungs (pneumonia)
Deferasirox (Exjade)	1750mg	OD, indefinite	Tablet for oral suspension	To treat the iron overload

Chorionic Gonadotropin (Gonasi®)	5000 I.U.	Three times a week (T.I.W.), indefinite	Subcutaneous injection	To stimulate the Leydig cells in the testes hence stimulating production of testosterone
Bumetanide	1mg	OD for 6 days	Oral tablet	Loop diuretic to treat the heart failure
Phenoxymethylpenicillin (Penicillin V)	500mg	OD, indefinite	Oral tablet	To prevent infection following splenectomy
Co-amoxiclav – following meropenem administration	375mg	TDS for 3 days	Oral tablet	To treat possible pneumonia
Amoxillin – following meropenem administration	250mg	TDS for 3 days	Oral tablet	To treat possible pneumonia

Diagnosis:

Being a known case of beta thalassemia, the presenting complaint of dyspnoea cough and lethargy indicated a complication of the condition. With the D-dimer being positive, the possibility of pulmonary embolism and DIC were considered. With the exclusion of pulmonary embolism using CTPA, it was concluded that the patient was experiencing complications of beta thalassemia leading to pulmonary hypertension, possible pneumonia and DIC. The patient was therefore administered intravenous antibiotics to treat the possible pneumonia and a loop diuretic to control the symptoms of pulmonary hypertension.

Final treatment and follow ups:

Following recovery after treatment for pulmonary hypertension, pneumonia and DIC, the patient was advised to stop smoking, stop binge drinking and reduce exertion. A follow-up appointment for right heart studies was given to the patient. A renal function test (urea, electrolytes, creatinine) to look for adverse effects of bumetanide (low sodium or rise in creatinine) was booked.

Fact Box 7:

Title: Beta Thalassemia Major (with pulmonary hypertension)

Pathophysiology:

Beta Thalassemia is a group of hereditary disorders of the blood which are characterised by aberrant expression of the beta haemoglobin genes, with Beta Thalassemia Major generally involving homozygosity for beta-zero (beta0) or compound heterozygosity for beta-plus (beta+) [1]. As a result of the mutations there is reduced synthesis of the beta chains of haemoglobin which leads to reduced levels of functional haemoglobin in the red blood cells, hence resulting in anaemia due to reduced oxygen carrying capacity of the red blood cells [1]. Because of this, the patient must undergo regular blood transfusions so that correct levels of functional haemoglobin are maintained in the blood. However, repeated blood transfusions lead to iron overload and eventually iron toxicity.

Although pulmonary hypertension (PH) is a complication of thalassemia, the incidence of the condition is not clear, with studies suggesting an incidence rate of 10%-75% in patients with Beta-thalassemia major [2-4]. While the pathophysiology of PH in beta-thalassemia patients is not clearly known, iron overload and deposition in the lungs, liver and heart together with a past history of splenectomy have all been associated with PH [2,5,6]. PH in such patients has been attributed to an increased response to vasoconstrictors as a result of an increased intracellular Ca^{2+} content secondary to potassium channel downregulation and endothelial injury in hypoxic conditions [2,7].

Evidence also suggests that chronic haemolysis plays a key role in the development of pulmonary hypertension in B-thalassemia. The haemoglobin released from the broken down red blood cells somehow scavenges nitric oxide. Hence, the removal of nitric oxide and the lowering of its concentration in the blood reduces its vasodilatory effect on hypoxic pulmonary vasoconstriction. Also, following the breakdown of red blood cells, the enzyme arginase is released. This breaks down arginine – the substrate for the synthesis of nitrogen monoxide. Both of these mechanisms contribute to an overall decrease in NO levels, resulting in a relative increase in endothelin-1 which is a potent vasoconstrictor. Hence this imbalance leads to the development of pulmonary hypertension [8].

Risk factors:

The risk factors which increase the probability that one develops this disease are mainly associated with genetic factors: Family history of thalassemia and certain ancestry.

Symptoms:

Beta Thalassemia Major is generally diagnosed at an early stage in infants of 6 to 24 months who fail to thrive and become pale together with possible enlargement of the liver and the spleen [1]. Beta Thalassemia Major may be attributed to jaundice and pallor, growth retardation, skeletal changes, extramedullary haematopoiesis (with possible mass development), abdominal swelling and hepatosplenomegaly [1].
Cardiac complications which may include cardiomyopathy secondary to iron deposition and myocarditis also increase the morbidity and fatality rate of the condition [8]. A significant contributor to such cardiogenic deaths in patients with Beta Thalassemia Major is the development of pulmonary hypertension, which is another complication of the condition [8].

Prevention:

Being a hereditary condition, the only method (so far) to prevent acquiring Beta Thalassemia is by population screening and genetic counselling.

Complications:

Together with the risks associated with Beta Thalassemia Major itself, the additional pulmonary hypertension may give rise to a number of complications [9]. These include[9]:

- Right-sided heart failure (cor pulmonale)
  Due to increased resistance in the pulmonary circulation, the right ventricle enlarges so as to be able to generate enough force which would allow enough blood to be perfused to the lungs. However, the thickening of the walls and the enlargement of the right ventricular chamber has a limit, beyond which, right-sided heart failure occurs.
- Blood Clots
  The pulmonary hypertension increases the risk that one develops blood clots within the vessels of the lung. These further increase the resistance, and hence contribute to the pulmonary hypertension. Apart from this, another complication which may arise is that these blood clots may dislodge from the pulmonary vessels and end up in the general circulation where they may cause obstruction of other vessels.
- Arrhythmia
  Irregular heartbeats of all chambers of the heart are possible complications of pulmonary hypertension. The arrhythmias may lead to palpitations, dizziness or fainting and can be fatal.
- Bleeding
  This is another fatal complication of pulmonary hypertension, where one starts bleeding into the lungs and eventually coughing up blood – haemoptysis.

Treatment

Management of Beta Thalassemia Major mainly involves regular transfusions for the correction of the anaemia, suppression of erythropoiesis and inhibition of iron absorption from the gastrointestinal system (to decrease iron overload) together with treatment of iron overload which occurs frequently in patients on regular transfusion [1]. The patients may therefore require the use of iron chelators and possible splenectomy while possible delayed puberty, hypogonadism and requirement of assisted reproduction should also be considered [1].

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