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Notes & Notes for MRCP
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• High total leucocyte count (TLC) leads to leucostasis and hyperviscosity drowsiness and retinal vein dilatation. • Blood film reveals white cells predominantly myeloblasts and promyelocytes. Poor prognostic features AML Cytogenetics Karyotype is of most prognostic value. •

> 60 years • 20% blasts after first course of chemo • cytogenetics: deletions of chromosome 5 or 7 bone marrow cytogenetics are the most important aspect in determining prognosis in AML Good prognostic features • Karyotype of bone marrow patients with t(8:21) or chromosomes 16 inversion have a low risk of relapse Classification - French-American-British (FAB) • MO - undifferentiated • M1 - without maturation • M2 - with granulocytic maturation the most common (25% of adult AML) associated with a t(8;21) translocation. • M3 - acute promyelocytic (APL) has the best prognosis of all the subtypes of AML. Unlike the other AML subtypes, APL is treated with all-trans retinoic acid (ATRA). t(15;17) • M4 - granulocytic and monocytic maturation associated with a t(16;16) translocation • M5 - monocytic • M6 - erythroleukaemia • M7 – megakaryoblastic AML (monocytic) M5: high count of circulating blasts may lead to symptoms of cellular hyperviscosity (headache, confusion, fits, coma) and tissue deposits of leukaemia cells (gums hypertrophy) with cells stain positive with Sudan Black and myeloperoxidase plus NES. ALL cells characteristically stain positive for PAS (Periodic acid-Schiff) and NSE (Non-specific Esterase). AML cells characteristically stain positive for Sudan Black and myeloperoxidase, but M4 and M5 cells stain positive for NSE, while M6 cells stain positive for PAS.

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Management • Combination chemotherapy including arabinosylcystosine after apheresis. • Cytarabine and Anthracycline is considered the initial treatment of choice for patients with AML.

Bone marrow transplantation • The aim would be to choose a fully matched sibling who was also CMV-negative. • In general, fully HLA matched, CMV matched, male donors are preferred over fully HLA matched, CMV matched female donors. This is because of the increased risk of graft versus host disease in stem cell donations from female donors to male recipients.

Acute promyelocytic leukaemia (APML) • APML, the M3 subtype of AML. • The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management • APML is associated with the t(15;17) translocation causes fusion of the PML and RAR-alpha genes. In 95% of cases, retinoic acid receptor-alpha (RARA) gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukaemia gene (PML) on chromosome 15. The mechanism underlying leukaemogenesis is aberrant fusion of 2 genes PML and RARA. Features • presents younger than other types of AML (average = 25 years old) • DIC or thrombocytopenia often at presentation • Auer rods (seen with myeloperoxidase stain) Auer rods are eosinophilic needle-like cytoplasmic inclusions found in blast cells • good prognosis management • treatment of APML differs from that of all other AML forms • the most appropriate initial treatment regimen: All trans retinoic acid (ATRA) a derivative of vitamin A., plus Anthracycline based chemotherapy

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The distinct elongated cytoplasmic structures are Auer rods which are pathognomonic for AML. Retinoic acid syndrome (or differentiation syndrome) Pathophysiology • thought to be the result of the release of cytokines and subsequent lung infiltration by the neutrophils created by the maturation of myelocytes in APML. • The presence of CD13 expression on leukemic cells can be a predictor of the future development of this syndrome. Causes • after treatment of APML with all-trans retinoic acid (ATRA) (present within a week of treatment) • after treatment of APML with arsenic trioxide. • usually occurs during induction therapy Incidence • 14-16% of patients. Features • dyspnea, pulmonary edema and effusions, A chest X-ray shows interstitial infiltrates. • fevers, • hypotension, • Other complications include pericardial effusion, renal insufficiency, and hypertension. treatment • Corticosteroids • the drug is temporarily stopped, then started again at 50-75% of the earlier dose. Alternatively, arsenic therapy can be tried. prognosis • Without prompt treatment with glucocorticoids, patients with this disorder have a mortality rate as high as 30% due to brain edema or hypoxemic respiratory failure. • Fortunately, most patients improve markedly within 12 hours and their symptoms resolved completely within 24 hours.

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Chronic myeloid leukaemia (CML) Pathophysiology • The Philadelphia chromosome is present in more than 95% of patients with (CML). • It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene

codes for a fusion protein which has tyrosine kinase activity in excess of normal Epidemiology • Sex: ♂ > ♀ • Peak incidence: 50–60 years Etiology • Idiopathic (in most cases) • Ionizing radiation (e.g., secondary to therapeutic radiation) • Aromatic hydrocarbons (especially benzene) Features • middle-age (40-50 years) • anaemia, • weight loss, • splenomegaly may be marked abdominal discomfort Complications • may undergo blast transformation (AML in 80%, ALL in 20%) Investigations • Peripheral blood spectrum of myeloid cells seen The blood film shows both mature (neutrophils) and immature forms in various stages of differentiation (myelocytes and metamyelocytes) In acute myelogenous leukemia (AML) one would expect only immature blasts. CML causes the most severe leukocytosis (> 500,000/µl) of all forms of leukemia Increasing basophilia is a sign of acceleration! • Cytogenetic analysis of the patient's bone marrow the most useful test most cases of CML are usually associated with BCR-ABL translocation, (Philadelphia chromosome) Better than molecular analysis of peripheral blood • Molecular analysis of peripheral blood useful and least invasive for the patient Chronic myeloid leukaemia – imatinib = tyrosine kinase inhibitor CML- Philadelphia chromosome – t(9:22) Philadelphia translocation, t(9:22) – good prognosis in CML, poor prognosis in AML + ALL

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 BCR-ABL translocation (t[9:22]) can be detected by PCR however, in practice one would still eventually proceed to a bone marrow (BM) examination to assess morphology and you would still also perform conventional cytogenetics on the bone marrow (this is done on a bone marrow sample rather than peripheral blood because the cellularity tends to be greater in the BM, giving lower failure rates of the test). • Leukocyte alkaline phosphatase (LAP) decreased Low LAP is a distinct feature of CML that distinguishes it from all other forms of leukemia WHO classification of the CML phases CML Phase Blast count in peripheral blood and bone marrow Chronic < 10% Accelerated 10–19% Blast ≥ 20% Management • Unlike (CLL), CML will progress to frank leukaemia quite rapidly, so treatment is needed. • imatinib is now considered first-line treatment inhibitor of the tyrosine kinase associated with the BCR-ABL defect very high response rate in chronic phase CML • If remission is not achieved with imatinib, then: in a patient under 60-65 years, an allogeneic transplant would be considered if there was a matched sibling donor; in a 50-year-old patient or younger a matched unrelated donor transplant would be considered too. • If the patient had been in blast crisis phase, then AML-type chemotherapy as well as Glivec (imatinib) would be the choice. • hydroxyurea • interferon-alpha • allogenic bone marrow transplant

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Allogenic bone marrow transplant Complication Cytomegalovirus pneumonia • The microscopy shows owl's eye inclusion bodies, characteristic of CMV, but diagnosis is usually made by PCR of blood/lavage fluid. • It is the commonest life-threatening complication following allogenic bone marrow transplant, • usually occurring within the first 4 months following surgery. • the treatment of choice Ganciclovir • Onset is rapid and mortality in the context of BMT is around 80%, even with antiviral therapy (ganciclovir).

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Hairy cell leukaemia Overview • malignant proliferation disorder of B cells. • Rare, about 2% of leukemias. • more common in males (4:1) • frequently occurs in men in their fifth decade. Features • pancytopenia • splenomegaly • skin vasculitis in 1/3 patients • 'dry tap' despite bone marrow hypercellularity • tartrate resistant acid phosphotase (TRAP) stain positive • characteristic hairy leukocyte on blood smear with a “fried egg” appearance medium-sized lymphocytes with numerous spiky, peripheral, cytoplasmic projections. Management • chemotherapy is first-line: cladribine (adenosine deaminase inhibitor), pentostatin Cladribine Cladribine is a purine analog inhibit DNA polymerase and cause DNA strand breaks. SE myelosuppression, nephrotoxicity, and neurotoxicity. • immunotherapy is second-line: rituximab, interferon-alpha Alpha interferon at 2 million U/m2 subcutaneously three times a week for 12-18 months can be used to salvage relapsed or refractory hairy cell leukemia.

Paraproteinaemia Causes of paraproteinaemia • myeloma • monoclonal gammopathy of uncertain significance (MGUS) • benign monoclonal gammopathy • Waldenstrom's macroglobulinaemia • amyloidosis • CLL, lymphoma • heavy chain disease • POEMS Benign monoclonal gammopathy • non-lymphoid malignancy (e.g. colon, breast) • infections (CMV, hepatitis) • autoimmune disorders (RA, SLE)

Multiple myeloma classic symptoms of multiple myeloma: bone pain, pathological fracture, anaemia and hypercalcaemia (leading to thirst). Multiple myeloma causes a low anion gap. Definition • Multiple myeloma is a neoplasm of the bone marrow plasma cells. Epidemiology • The peak incidence is patients aged 60-70 years.

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• Multiple myeloma is the most common primary tumor of the bone in patients older than 50 years. • equal sex ratio • more common in Afro-Caribbean ethnic groups than in Caucasians Monoclonal products produced • IgG (50-60%) • IgA (20-30%) • light chain disease (20%) Association • Type 2/Proximal renal tubular acidosis is a type of renal tubular acidosis associated with multiple myeloma. Pathophysiology • Neoplastic proliferation of plasma cells Bone marrow infiltration → suppression of hematopoiesis → leukopenia, thrombocytopenia, anemia Cell proliferation → osteolysis → hypercalcemia • Overproduction of monoclonal immunoglobulin and/or light chains Non-functioning antibodies → functional antibody deficiency ↑ Serum viscosity → hyperviscosity syndrome Clinical features • bone disease: due to neoplastic plasma cells activating RANKL receptors on osteoclasts. bone pain, (Bones commonly affected are the flat bones of the spine, and as such lower back pain is one of the most common presenting features) osteoporosis + pathological fractures (typically vertebral), osteolytic lesions weakness and paresthesias in the lower extremities due to vertebral compression fractures • anaemia fatigue and malaise The most common presenting manifestations of multiple myeloma are those related to anemia. • infection • hypercalcaemia nausea, fatigue, confusion, polyuria, constipation • hyperphosphataemia due to reduced renal excretion which may be directly due to renal

impairment or interference with excessive protein load. • Foamy urine, caused by Bence Jones proteinuria • renal failure the most common cause is from light chain deposition. Usually, the renal damage in MM is tubular. Occasionally there may be glomerular damage with consequent albumin loss. • amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity carpal tunnel syndrome - the most common peripheral neuropathy associated with multiple myeloma • Multiple myeloma may present with roleaux formation on blood film and raised total protein (globulin component). The globulin level is markedly raised (albumin + globulin = total protein), suggesting the presence of a paraprotein. (globulin level = total protein - albumin). A normal level should be below 36 g/L. • Hypercalcaemia in myeloma primary factor:

 due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels Which acid-base disorders may be found in an IgG multiple myeloma? Low anion-gap metabolic acidosis IgG tends to be cationic, whereas IgA tends to be anionic. As a consequence, patients with IgG myeloma will tend to have a lower than normal serum anion gap. Diagnostic criteria for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma. • Major criteria Plasmacytoma (as demonstrated on evaluation of biopsy specimen) 30% plasma cells in a bone marrow sample Elevated levels of M protein in the blood or urine monoclonal proteins: in the serum (usually IgG or IgA) in the urine (Bence Jones proteins) there is Negative dipstick for protein and positive in biochemistry, because Bence jones proteins are not detected by dipstick
• Minor criteria 10% to 30% plasma cells in a bone marrow sample. Minor elevations in the level of M protein in the blood or urine. Osteolytic lesions (as demonstrated on imaging studies). Low levels of antibodies (not produced by the cancer cells) in the blood. Investigations: (NICE 2016) 1. to confirm the presence of a paraprotein indicating possible myeloma or (MGUS): serum protein electrophoresis and serum-free light-chain assay (best initial test) serum protein electrophoresis If serum protein electrophoresis is abnormal use serum immunofixation Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) alone to exclude a diagnosis of myeloma. The observation that serum free light chains can occur in the absence of a detectable monoclonal protein in the peripheral blood is the explanation why two tests must always be done when investigating possible myeloma: both serum electrophoresis and either serum or urinary free light chains. monoclonal free light chains are found in isolation in 20–30% of cases of myeloma 2. to confirm a diagnosis of myeloma: bone marrow aspirate and trephine biopsy the bone marrow aspirate would confirm the diagnosis irrefutably. morphology to determine plasma cell percentage Bone marrow examination would reveal increased plasma cells (greater than 4% and usually greater than 30%). flow cytometry to determine plasma cell phenotype bone marrow aspirate dark red jelly-like material in the syringe (Plasma cells)

3. in a patient presenting with spinal cord compression: the most appropriate initial investigation is Urgent MRI of her spine This should be done before investigation that used to confirm myeloma. skeletal survey bone lesions Treatment: general view • The best initial treatment of multiple myeloma is chemotherapy induction. • autologous bone marrow transplant in addition to chemotherapy has better results than chemotherapy alone. • Asymptomatic patients: watch and wait, unless patients have: ≥ 60% clonal cells, excessive free light chains or ≥ 1 bone lesion • Symptomatic patients HCT eligible: induction therapy followed by autologous HCT HCT ineligible: chemotherapy alone (e.g., dexamethasone and lenalidomide) • Supportive therapy Osteolysis and bone pain Bisphosphonates Radiation therapy of osteolytic regions Pancytopenia with anemia and increased risk of infection Blood transfusions Granulocyte-colony stimulating factor (G-CSF) and erythropoietin (EPO) Patients with myeloma with high paraprotein levels and symptoms related to hyperviscosity should have urgent plasma exchange, chemotherapy needs to then be instituted promptly to control the disease process and prevent symptoms reoccurring.

Haematology&Oncology Treatment • previously untreated multiple myeloma (newly diagnosed) Patients who are eligible for high-dose chemotherapy with stem cell transplantation bortezomib + dexamethasone, or bortezomib + dexamethasone + thalidomide if high-dose chemotherapy with stem cell transplantation is considered inappropriate thalidomide + alkylating agent + corticosteroid • People who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation: bortezomib (a proteasome inhibitor) monotherapy • People who have received two or more prior therapies: lenalidomide + dexamethasone lenalidomide immunomodulatory derivatives (structural derivatives of thalidomide) • People with untreated, newly diagnosed, myeloma-induced acute renal disease: bortezomib + dexamethasone If a bortezomib is unsuitable thalidomide + dexamethasone Do not perform plasma exchange for myeloma-induced acute renal disease. • Preventing bone disease, managing non- spinal and spinal bone disease bisphosphonates should be given routinely, even in the absence of hypercalcaemia. Bisphosphonates reduce bony disease in myeloma, lowering the frequency of pathological fractures, modulate the disease and have some antitumor activity. zoledronic acid or disodium pamidronate, if zoledronic acid is contraindicated or not tolerated or sodium clodronate, if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or not suitable surgical stabilisation followed by radiotherapy for non-spinal bones that have fractured or are at high risk of fractures. Consider radiotherapy for people who need additional pain relief • Managing peripheral neuropathy If patient on bortezomib switch to subcutaneous injections and/or reduce to weekly doses and/or reduce the dose. if patient on other than bortezomib Temporarily stop neuropathy-inducing myeloma treatments if people develop either of the following: grade 2 neuropathy with pain grade 3 or 4 neuropathy • Managing fatigue Erythropoietin analogues (adjusted to maintain a steady state of haemoglobin at 110–120 g/litre) to improve fatigue in people with

myeloma who have symptomatic anaemia. • Cord compression secondary to bony involvement of multiple myeloma: I.V Steroids should be commenced immediately Melphalan and dexamethasone both have a place in the treatment of myeloma but would not be of use as pain control. However, the treatment of choice is local radiotherapy. NICE suggest localised radiotherapy should be the first point of call for urgent treatment. Radiotherapy is extremely effective as pain control in this situation and would be the ideal choice. Vertebroplasty is typically considered in patients of whom have evidence of metastatic changes in the spine but show no signs of spinal cord compression.

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 Surgical decompression: is also considered if imaging suggests any form of spinal instability or structural defects, but often after steroids and radiotherapy has been administered. Blood transfusion in myeloma may cause acute deterioration • The plasma volume increases with increasing viscosity and may compromise cardiac function. • They should not be transfused until the viscosity has been lowered as a rise in haematocrit can precipitate a serious worsening of their symptoms. Thalidomide • Immunomodulatory drugs such as thalidomide and lenalidomide are now first line medications in the treatment of myeloma. • The most common side effect of lenalidomide is myelosuppression, whereas somnolence, peripheral neuropathy and constipation are side effects of thalidomide. • The inherent, serious issue that is applicable to both medications is the teratogenic potential - all patients must be informed of this risk and advised regarding birth control and avoidance of sharing of medications with any other person. • It is not known whether lenalidomide is present in the semen of male patients receiving the drug. Therefore, males receiving lenalidomide must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy. Myeloma: prognosis • B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. Beta-2-microglobulin has been shown to be predictive of risk of progression of disease in myeloma, myelodysplastic syndrome, and chronic myeloid leukaemia. In myeloma it is an accurate estimate of total disease load, with guidelines suggesting that a beta-2-microglobulin level of >3.5 mg/L is strongly associated with increased mortality and morbidity. • Low levels of albumin are also associated with a poor prognosis • Increased lactate dehydrogenase levels more than double the normal is considered a bad prognostic sign in multiple myeloma. International prognostic index Stage Criteria Median survival (months) I B2 microglobulin < 3.5 mg/l Albumin > 35 g/l

II Not I or III

III B2 microglobulin > 5.5 mg/l

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Haematology&Oncology Abnormal serum protein electrophoresis pattern in a patient with multiple myeloma. Note the large spike in the gamma region. • In the interpretation of serum protein electrophoresis, most attention focuses on the gamma region(gamma-globulin zone), which is composed predominantly of antibodies of the IgG type.

Monoclonal gammopathy of undetermined significance (MGUS) • MGUS also known as benign paraproteinaemia and monoclonal gammopathy) is a common condition that causes a paraproteinaemia and is often mistaken for myeloma. Differentiating features are listed below. • can be seen in >5% of people over 70 years of age. Risk of transmission to malignancy: • Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years • 1 percent per year develop multiple myeloma. Features • usually asymptomatic • no bone pain or increased risk of infections • around 10-30% of patients have a demyelinating neuropathy Differentiating features from myeloma • normal immune function • normal beta-2 microglobulin levels • lower level of paraproteinaemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA) • stable level of paraproteinaemia • no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease) feature MGUS myeloma M protein concentration in serum <30 g/l

> 30 g/l bone marrow plasma cells <10 % 10 % organ and tissue impairment no end organ damage including bone lesions organ or tissue impairment (including bone lesions)

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Treatment • Observation • if there is neuropathy MGUS patients are associated with osteoporosis and osteopenia. They may benefit from treatment with bisphosphonates Bisphosphonates pyrophosphate analogue act by binding to hydroxyapatite in bone which leads to low osteoclastic activity. MRCPUK-part-2-March- 2017: A 72-year-old man C/O persistent tiredness over the past 3 months. No other abnormality. Investigations reveals Albumin: 38 g/l, IgG paraprotein band: 14 g/l, Bone marrow: 7% plasma cells. Which of the following is the most appropriate intervention? Observation MGUS is defined by paraprotein (<30 g/l), bone marrow plasma cells <10% and the absence of myeloma-related organ or tissue damage (predominantly renal, skeletal or bone marrow impairment). Annual overall progression to myeloma is 1% and, as such, no intervention is required. Smoldering myeloma • Smoldering multiple myeloma multiple myeloma (M-protein >3g/dL or >10% plasma cells in bone marrow) + no end organ damage. • criteria for end-organ damage, which are: Serum calcium >11.5 mg/dL Serum creatinine >2 mg/dL or estimated creatinine clearance <40 ml/min Anemia with hemoglobin <10 g/dL Bone lesions: osteolytic, pathological fracture; osteopenia • Treatment Observe and monitor Non-secretory myeloma • Bone marrow clonal plasma cells =10%, Myeloma-related end-organ damage, No M protein in blood or urine

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Thymoma are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life. Associated with • myasthenia gravis (30-40% of patients with thymoma) • red cell aplasia • dermatomyositis • also : SLE, SIADH Causes of death • compression of airway • cardiac tamponade

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Tumour lysis syndrome (TLS) • Tumour lysis syndrome (TLS) is a potentially deadly condition Causes: • treatment of high grade lymphomas and leukaemias. • It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy. Pathophysiology: • breakdown of the tumour cells and the subsequent release of chemicals from the cell. Features: • high potassium • high phosphate • low calcium. • It should be suspected in any patient presenting with an acute kidney injury in the presence of a high phosphate and high uric acid level. Diagnosis: • From 2004 TLS has been graded using the Cairo-Bishop scoring system - Laboratory tumor lysis syndrome: abnormality in two or more of the following, occurring within three days before or seven days after chemotherapy. uric acid > 475umol/l or 25% increase potassium > 6 mmol/l or 25% increase phosphate > 1.125mmol/l or 25% increase calcium < 1.75mmol/l or 25% decrease • Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following: increased serum creatinine (1.5 times upper limit of normal) cardiac arrhythmia or sudden death seizure Management of acute tumour lysis syndrome • aggressive hydration, aiming for 3 L/m2 control of electrolyte disturbances (typically, hypocalcaemia, hyperphosphataemia, hyperkalaemia and uraemia) • clearance of the increased metabolic load with rasburicase, a specific recombinant enzyme. Prevention: • Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy. Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys. The commonest reported side effect of rasburicase is fever. rasburicase overdose may lead to accumulation of hydrogen peroxide. • patients at low risk oral allopurinol during chemotherapy • Other options for the management of tumour lysis syndrome include Acetazolamide to drive urine alkalinisation.

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Waldenstrom's macroglobulinaemia Overview • It is a lymphoplasmacytoid malignancy seen in older men, characterised by the secretion of a monoclonal IgM paraprotein, • indolent B-cell lymphoma • Also known as Lymphoplasmacytoid lymphoma • most common in older white men Pathophysiology • monoclonal IgM production by a malignant lymphoplasmacytic clone that can cause damage to multiple organs. • The tumor cells in Waldenstrom macroglobulinemia are positive to CD20 markers. Features • monoclonal IgM paraproteinaemia • systemic upset: weight loss, lethargy • hyperviscosity syndrome e.g.: visual disturbance, neurological symptoms such as headache, dizziness, and vertigo raynaud phenomenon • Bleeding is a possible complication as viscous serum causes defective platelet aggregation. • hepatosplenomegaly • lymphadenopathy • cryoglobulinaemia e.g. Raynaud's Investigations • protein electrophoresis elevated IgM • Bone marrow biopsy (the gold standard for the diagnosis) Shows abnormal plasma cells with Dutcher bodies (intranuclear inclusions of IgM deposits) • Plasma viscosity plasma viscosity measurement is essential to diagnose and initiate treatment. The initial treatment would be plasmapheresis followed by cytoreductive therapy. Differential diagnosis • multiple myeloma usually presents with IgG or IgA secretion and lytic bone lesions. • Waldenström’s In

an elderly patient found to have a large IgM–kappa paraprotein, which feature will help to decide whether it is related to Waldenström’s macroglobulinaemia? No isotype suppression Isotype suppression (normal IgG and IgA levels) is more a feature of myeloma than Waldenström’s macroglobulinaemia and is therefore a good differentiator. Treatment • Asymptomatic Follow-up treatment only indicated in symptomatic patients • Causative: CD20 antibodies (e.g., rituximab) • Hyperviscosity syndrome: plasmapheresis

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ECOG score • The ECOG score (Eastern Cooperative Oncology Group (ECOG) score) is a 'performance status' scale, or a score that measures the functional status of a patient. • It is used to decide if a patient is a good or poor candidate for future oncological therapies. • Those with a poor functional status is a poor candidate for further chemotherapy.

Fully active, able to carry on all pre-disease performance without restriction

Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours

Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours

Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

Dead

Tumour markers Tumour markers may be divided into: • monoclonal antibodies against carbohydrate or glycoprotein tumour antigens • tumour antigens • enzymes (alkaline phosphatase, neurone specific enolase) • hormones (e.g. calcitonin, ADH) It should be noted that tumour markers usually have a low specificity Monoclonal antibodies Tumour marker Association CA 125 Ovarian cancer primary peritoneal cancer CA 19-9 Pancreatic cancer CA 15-3 Breast cancer

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Tumour antigens Tumour marker Association Prostate specific antigen (PSA) Prostatic carcinoma Alpha-feto protein (AFP) Hepatocellular carcinoma, teratoma , non-seminomatous germ-cell tumours Carcinoembryonic antigen (CEA) Colorectal cancer S-100 Melanoma, schwannomas Bombesin Small cell lung carcinoma, gastric cancer, neuroblastoma β-human chorionic gonadotrophin choriocarcinomas, germ-cell tumours and lung cancers • Bence Jones protein

specific for myeloma. false positives are rare, and therefore it is more specific than the other markers. The most specific tumour marker • Alpha-fetoprotein (AFP), beta-hCG and PLAP (placental like isoenzyme of alkaline phosphatase) are the major tumour markers in use for the monitoring of testicular teratoma. Common tumor markers Tumor marker Associated conditions Alpha fetoprotein (AFP) • Hepatocellular carcinoma (HCC) • Hepatoblastoma • Yolk sac tumor of the ovary (endodermal sinus tumor) • Mixed germ cell tumor • Transient elevation during pregnancy • ↑AFP: abdominal wall defects, neural tube defects • ↓AFP: associated with trisomy 21, 18, and 13 (See prenatal diagnostics for details) β-HCG • Testicular germ cell tumors (choriocarcinoma, embryonal cell carcinoma, mixed germ cell tumor, seminoma) • Ovarian cancer: choriocarcinoma (gestational trophoblastic disease) • If detectable in urine • Pregnancy marker • Molar pregnancy (hydatidiform mole) Carcinoembryonic antigen (CEA) • Colorectal cancer • Pancreatic cancer • Breast cancer • Lung cancer (especially in non-small cell cancers)

Common tumor markers Tumor marker Associated conditions • Gastric cancer • Endometrial cancer • Medullary thyroid cancer • Smokers Prostate-specific antigen (PSA) • Prostate cancer • Benign prostatic hyperplasia • Prostatitis Calcitonin • Medullary thyroid cancer Alkaline phosphatase • Metastases to bone or liver • Paget disease of the bone Lactate dehydrogenase (LDH) • Ovarian cancer (dysgerminoma) • Testicular germ cell tumors (both seminoma and nonseminoma) • Lymphomas • Ewing's sarcoma • Hepatitis • Hemolysis • Myocardial infarction Neuron specific enolase (NSE) • Small cell lung cancer • Neuroendocrine tumors • Neuroblastoma • NSE is released secondary to brain injury (e.g., stroke) CA 19–9 • Pancreatic adenocarcinoma CA 15–3/CA 27–29 • Breast cancer CA 125 • Ovarian carcinoma(80–100%) Chromogranin A • Neuroendocrine tumors • Medullary thyroid cancer S-100 protein (S100A) and (S100B) • Malignant melanoma β2 microglobulin (β2M) • Multiple myeloma • Chronic lymphocytic leukemia • Renal disease Thyroglobulin • Papillary thyroid carcinoma • Follicular thyroid carcinoma Monoclonal immunoglobulins • Multiple myeloma • Waldenstroms macroglobulinemia • Monoclonal gammopathy • Infections • Certain autoimmune conditions (e.g., rheumatoid arthritis)

Neutropenic sepsis (Febrile neutropenia) Definition • Neutropenic sepsis is a relatively common complication of cancer therapy (chemotherapy). • It most commonly occurs 7-14 days after chemotherapy. • It may be defined as a neutrophil count of < 0.5 * 109 in a patient who is having anticancer treatment and has one of the following: a temperature higher than 38 C or other signs or symptoms consistent with clinically significant sepsis Causes • in the majority of them identifying a source of the temperature can be impossible. • the most common pathogens are now gram-positive organisms. such as Staphylococcus epidermidis or Streptococcus viridans (around 60% of cases) • Source of infection In neutropenic patients, almost any site can be the source. Indwelling lines Staph.epidermidis infection mucositis or previous quinolone treatment

viridans streptococci Risk factors • Age > 65 • Albumin less than 35 g/l • Hepatic disfunction • Baseline neutrophil less than 1.5 * 109 • Planned relative dose intensity > 80% Prophylaxis • if it is anticipated that patients are likely to have a neutrophil count of < 0.5 * 109 as a consequence of their treatment they should be offered a fluoroquinolone Management • antibiotics must be started immediately, do not wait for the WBC,(N.B. after taking cultures). • First-step: NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately piperacillin with tazobactam with gentamicin is the preferred first-line option according to Christies guidelines for patient who are not allergic to penicillin and have no significant renal impairment. If there is penicillin allergy meropenem 1g three times a day is an appropriate option Dose adjustment may be needed where the GFR is less than 50 ml/min many units add vancomycin if the patient has central venous access, but NICE do not support this approach assessment the patient at 48 hours, If they have improved and the temperature has settled Convert patient to oral antibiotics and discharge Mucositis can be a source of neutropenic sepsis Swab mouth ulcer Neutropenic patients should avoid cold meats, soft cheese and dairy products due to risk of listeriosis

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 NICE does not recommend keeping patients in hospital whilst waiting for their neutrophil count to improve. • Second-step: if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin • Third-step: if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting antifungal therapy blindly • there may be a role for G-CSF (filgrastim) in selected patients if the neutropenic sepsis has responded well to treatment, but is still neutropenic, could be given G-CSF to stimulate a neutrophilia to help restore his cell counts quicker and reduce the chance of developing another episode of neutropenic sepsis. Side-effect of G-CSF (filgrastim): Filgrastim stimulates a white cell count which can increase far above the normal range, and the white cell count will return to normal once it is stopped. MRCPUK-part-1-May 2016 exam: When is the risk of febrile neutropenia thought to be highest following chemotherapy? 10 days in to treatment

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Assessment of neutropenia Definition and classification • absolute neutrophil count (ANC) <1500/microlitre or <1.5 x 10^9/L is defined as neutropenia and graded as mild, moderate, severe, or very severe: Mild: 1000 to 1500/microlitre or 1 to 1.5 x 10^9/L Moderate: 500 to 999/microlitre or 0.5 to 0.99 x 10^9/L Severe: 200 to 499/microlitre or 0.2 to 0.49 x 10^9/L Very severe: <200/microlitre or <0.2 x 10^9/L. • As the ANC falls below 1000/microlitre or 1 x 10^9/L, the risk of infection progressively increases. • If the ANC falls below 500/microlitre or 0.5 x 10^9/L, infections may be life-threatening. However, there are some diseases, such as autoimmune neutropenia (AIN), in which a low ANC does not confer an infection risk; infections are rare in these patients despite the ANC often being <500/microlitre or <0.5 x 10^9/L. • The ANC varies according to age and ethnicity. It is lower in children than in adults. Black people and some Arab populations display lower average values. The normal range in black people has a

lower limit of 1400/microlitre or 1.4 x 10^9/L. Gram colony stimulating factor (G-CSF) can be used to boost neutrophil numbers in neutropenia Neutropenic sepsis with no response to antibiotics at 48 hrs possible fungal infection

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Causes • Infections (the most common causes of neutropenia in adults), • drug-induced neutropenias • Acquired bone marrow diseases such as the leukaemias, lymphomas, and aplastic anaemia • nutritional deficiencies (vitamin B12, folate, copper)

Systemic mastocytosis Systemic mastocytosis results from a neoplastic proliferation of mast cells Features • urticaria pigmentosa - produces a wheal on rubbing (Darier's sign) • flushing • abdominal pain • monocytosis on the blood film Diagnosis • raised serum tryptase levels • urinary histamine

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Cervical cancer • Cervical cancer is the most common cancer worldwide • The incidence of cervical cancer peaks around the 6th decade. • It may be divided into squamous cell cancer (80%) adenocarcinoma (20%) Features • may be detected during routine cervical cancer screening • abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding • vaginal discharge Risk factors • human papilloma virus (HPV) 16,18 & 33 the most common associated with HPV 16 and 18 in approximately 70% of cases. New vaccines are currently available in the United Kingdom to help immunise against this virus and hopefully prevent future cases of cervical cancer. • smoking • human immunodeficiency virus • early first intercourse, many sexual partners • high parity • lower socioeconomic status • combined oral contraceptive pill* *the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov confirmed the link Mechanism of HPV causing cervical cancer • HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively • E6 inhibits the p53 tumour suppressor gene • E7 inhibits RB suppressor gene

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Ovarian tumours Ovarian cancer screening is not recommended in the general population as no survival benefit from earlier diagnosis and therapy has been shown. • germ cell tumours Patients are usually young. most commonly seen in adolescents due to embryologic remnants early pulmonary metastases The fact that this lady is young, and has early pulmonary metastases, make a germ cell tumour much more likely • The diagnosis is usually made on biopsy in the case of ovarian tumours. • treatment usually consists of surgery followed by chemotherapy (BEP). • Epithelial cell tumours usually disseminate through the abdomen and peritoneum prior to metastasising to the lungs. • Markers such as AFP, β-human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH) may be raised the most sensitive marker used for monitoring

treatment efficacy and risk of relapse is AFP. • Treatment of ovarian cancer: Patients with low risk, early-stage ovarian cancer (stage I, grade 1 disease confined to one or both ovaries with an intact capsule and no ascites) after thorough surgical staging have a greater than 90% cure rate with surgery alone and close observation is required. Platinum-based therapy, such as intravenous carboplatin and paclitaxel, is warranted for high risk, early-stage ovarian cancer (stage IC or II, grade 3 tumour or clear cell histology). Intraperitoneal chemotherapy is indicated for patients with stage III disease Debulking surgery followed by chemotherapy is proven to be the best treatment option in patients with peritoneal carcinomatosis from ovarian cancer. Intraperitoneal chemotherapy has less toxicity compared to IV chemotherapy and is better tolerated. • A young man with a germ cell tumour (raised β-HCG) can expect a greater than 95% cure rate, especially with seminomas. • β-HCG is the best tumour marker confers the best prognosis

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_Breast cancer The triple assessment of a breast lump is essential to diagnose a breast lump accurately. It involves;

1. physical examination,
2. mammography and then
3. ultrasound guided fine needle aspiration (FNA).

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Risk factors • inherited BRCA-1 mutation (or BRCA-2) the greatest risk BRCA1/2 carriers have a 40–70% chance of getting breast cancer by age 70, and a 10–70% chance of getting ovarian cancer by age 70. family history of breast cancer at a young age makes this more likely. What is the DNA repair mechanism by which the BRCA1 and BRCA2 proteins act? Double strand DNA break repair BRCA involved in repair of double strand DNA breaks by homologous recombination. • Early menarche • late menopause due to increased hormone exposure throughout life. • Nulliparity • Oral contraceptive use is also associated with a slight increase in risk of developing breast and also endometrial cancer. What is the best predictive factor for local recurrence of breast cancer after surgery, chemotherapy and radiotherapy? Age Patients below the age of 40 are significantly more likely to develop local recurrence of a breast cancer than those aged 41+. Screening • Mammograms screening sensitive in older (because of less dense breast tissue) not sensitive in younger (because of denser breast tissue) MRI and ultrasound are better in them. In young patients with a BRCA mutation, mammographic screening has a low sensitivity for detecting tumours • Mammographic screening of all women between the ages of 50 and 70 years can reduce mortality from breast cancer by 25%. There is no evidence for routine screening below this age. • mutation of BRCA1 or BRCA2 gene increases the risk of breast cancer should be screened at younger than 50 years. Breast MRI is used for patients with invasive breast cancer in the following circumstances: • if there is a discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment • if breast density precludes accurate mammographic assessment • to assess tumour size if breast conserving surgery is being considered for invasive lobular cancer

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• Staging CT is not used routinely in primary breast cancer, only if there is suspicion of metastatic spread. Tumour marker • CA15-3 tumour marker are used to assess disease activity in metastatic breast cancer Management • Breast-conserving therapy lumpectomy with sentinel lymph node biopsy followed by breast irradiation indicated for patients with focal disease randomised clinical trials have shown that the survival rate for women undergoing breast-conserving therapy is equivalent to that of those who undergo mastectomy, breast-conserving therapy resulting in improved cosmetic outcomes and less morbidity than mastectomy. Most patients treated with lumpectomy without radiation therapy have a high risk for local recurrence. Sentinel lymph node biopsy is safe and adequate for screening the axillary lymph nodes for metastases in women with small breast tumours. • Mastectomy indicated in patients in whom complete excision cannot be achieved unless mastectomy is performed or radiation is contraindicated. • Adjuvant radiotherapy is recommended by (NICE) given after wide local excision of a breast tumour to reduce the risk of local recurrence. There is growing evidence that adjuvant radiotherapy also increases survival for those patients at high risk of relapse. There is however a risk of increased cardiovascular mortality after 15-20 years, which may be reduced with the use of modern techniques such as conformal radiotherapy and intensity-modulated radiotherapy. Wound healing can be reduced after radiotherapy, and a period of at least a few weeks is usually given between surgery and initiation of radiotherapy. • Prophylactic mastectomy is indicated only in patients with BRCA1 or BRCA2. Drug therapy • Hormonal treatment is used to remove the proliferative stimulus of oestrogen from tumour cells. • Tamoxifen is used for adjuvant hormone treatment in pre-menopausal women first line. Tamoxifen acts by blocking the binding of oestrogen to its receptor within the nucleus. In patients with oestrogen receptor-positive tumours, tamoxifen therapy for five years in addition to lumpectomy decreases the risk of a new breast cancer event. long-term use is associated with: vaginal bleeding, endometrial thickening and increased risk of endometrial cancer

 thromboembolism. The lack of oestrogen receptor staining suggests a poor response to hormonal therapy with tamoxifen. • Anastrozole is used for adjuvant hormone treatment in post-menopausal women first line. aromatase inhibitor Three aromatase inhibitors are licensed for treatment of early oestrogen-receptorpositive breast cancer:

1. anastrozole,
2. exemestane,
3. letrozole. Aromatase inhibitors work by preventing peripheral conversion of oestrogen and therefore cause profound oestrogen deprivation in a post-menopausal woman. This increases the risk of osteoporosis and fragility fractures. A DEXA scan must be done at the start of treatment to identify those patients in whom a bisphosphonate must be considered for bone protection. Aromatase inhibitors can be continued in a patient who has suffered no fragility fractures providing adequate measures are taken for bone

protection, for example, prescribing a bisphosphonate. In patients who suffer a fragility fracture tamoxifen must be considered as this does have a partial oestrogen agonist action on bone, reducing the risk of osteoporosis. A common side-effect is reduced bone mineral density, and bone densitometry is therefore often carried out prior to and during treatment. Anastrozole is currently indicated for early oestrogen-receptor-positive breast carcinoma at a dose of 1 mg daily for 5 years. • Fulvestrant is a new pure anti-oestrogen agent which appears to be as effective as anastrozole. It is given by sub-cutaneous injection once every three weeks. mechanism of action Selective oestrogen receptor down regulator has been shown to be equivalent to anastrazole in terms of efficacy. Fulvestrant is the only endocrine agent currently available that can be given parenterally, which offers significant advantages to patients with swallowing difficulties. Fulvestrant is not currently given first line in post-menopausal women but this may change in the near future. • The positive C-erb B2 (HER2/neu) staining suggests that trastuzumab (Herceptin) may be effective. Several randomised trials have demonstrated that 52 weeks of adjuvant trastuzumab therapy reduces the risk for breast cancer recurrence in women with HER2 overexpression by approximately 50% and may even reduce mortality by as much as 30%.