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Annex 1: a transcript of the case-based panel discussion under pathologic diagnosis of MM
Case 1
Question 1: what are the other mimics of myeloma on morphology? **Response: Dr. Simon Onsongo:** plasmacytoid lymphomas, but consider all the other investigations including clinical, biochemistry and radiology to give appropriate diagnostic results. Morphological analysis alone may not be sufficient to establish a diagnosis.
Question 2: are there cases where the bone marrow aspirate (BMA) is normal but Trephine biopsy shows features of myeloma and vice versa? **Response: Dr. Simon Onsongo:** do both BMA and trephine to have a higher chance of obtaining the correct diagnosis. In cases where BMA is inadequate/hemodilute/normal, if a trephine sample was obtained then it will come in handy. In most cases if you have adequate material on both BMA and trephine then the results should be consistent. Different results may be due to obtaining inadequate sample on either one of the above.
Question 3: is there a scenario where a patient could be having normal BMA/Trephine results, normal SPEP/SFLC ratio but the patient has CRAB symptoms? **Response: Dr. Simon Onsongo:** I don't think so. The CRAB symptoms occur because of plasma cells increasing and producing monoclonal proteins and causing biochemical disturbances that manifest as CRAB symptoms.
Question 4: is there a scenario whereby a patient could be having a normal BMA/Trephine results and yet has increased M-component on SPEP and also has CRAB symptoms? **Response: Dr. Simon Onsongo:** this is unlikely; the m-component is because of increased proteins produced by the abnormal plasma cells population which will manifest clinically. In my experience with diagnosis of MM it is critical to obtain a wide array of tests: pathology, biochemistry, haematology and radiology and frequently our patients are not able to afford all these tests at once and this leads to delays in diagnosis.
Question 5: what do you mean by a sample being insufficient, hemodilute, and describe an adequate sample for aspirate and trephine analysis? Please also comment on an appropriate site for obtaining a bone marrow sample. **Response: Dr. Valarie:** insufficient sample means you did not get bone marrow particles enough to report on bone-marrow morphology either because it is a dry-tap, we don't see any particles for your aspirate. For a trephine biopsy, its usual with regards to the length of the core, the ideal length is 2 cm but a coreless than 1 or 0.5 may be considered inadequate to give a diagnosis**.** Hemodilute is when you've tried multiple types but you don't get the particles because they have been contaminated by the peripheral blood. 1 cm for paediatric and for adults 2 cm is an adequate sample for BMAT analysis. It is recommended that you do the trephine first followed by the aspirate.
Question 6: is low platelet count a contraindication for bone marrow aspiration procedure? **Response: Dr. Valerie:** no it is not. A lot of the times the low platelets could be as a result of the disease process hence the need to obtain a diagnosis. Do not be afraid, apply pressure to stop the bleeding then resume the procedure to ensure you obtain a sample. If pressure is applied for long enough bleeding often stops.
Question 7: when performing a bone marrow aspirate how many times should you attempt in one sitting? Dry tap? Comment on appropriate site for BMA in Myeloma patients. **Response: Dr. Valerie:** this is a difficult scenario. Always prepare to do both BMA and trephine; you may prepare to convert to a trephine. Although it poses a challenge because it means that a trephine needle should be available which is not always the case in public facilities because of cost.
Question 8: please comment on an appropriate site for obtaining a bone marrow sample. **Response: Dr. Valerie:** an appropriate and safest site for BMA in adult is posterior superior iliac spine because it is an easy site to access. What about anterior superior iliac spine? Occasionally I have been forced to use this site in obese patients but I prefer the posterior superior iliac spine; this is the safest site.

Is it necessary to take bone marrow samples from bilateral sites even if the first site you sampled produced enough sample?

Response: Dr. Valerie/Dr. Simon: no there is no need to take a second sample if the first was sufficient. This used to be the practice for lymphoma but is falling out of favour. A unilateral sample is enough to obtain a diagnosis. What about sternal BMA?

Response: Dr. Valerie: I rarely do sternal aspirates. There is a lot of room for risk. You may inadvertently end up doing pericardial tap. Besides, you cannot convert a sternal aspirate to a trephine in case you have a dry tap.

Question 9: are there times when you are required to use BMA to follow up a patient on treatment for Myeloma?

Response: Dr. Valarie yes. If you have flow cytometry the BMA can be used to establish minimal residual disease or the trephine can be used for immunohistochemistry.

Question 10: how crucial is patient cooperation during bone marrow sample collection? Does failure to sedate a patient during the procedure affect the quality of the sample collected?

Response: Dr. Valarie: very crucial. It is important to talk to the patient and let them know what to expect. Take them through the process that they will experience, a pinch as you insert the needle, then there will be numbing when the local anaesthetic takes effect, a little discomfort as you penetrate the bone and when withdrawing the needle and that's it. Also ensure you use adequate amount of local anaesthetic so that the patient doesn't have a traumatic experience. Remember that in haematological malignancies the patient will have many bone marrow procedures so you don't want them to miss an appointment because the procedure was so painful.

Response: Dr. Lotodo: from my experiences often times when a patient feels some pain as you aspirate, I find that it is likely that I have aspirated enough sample.

Response: Dr. Beatrice Melly: when you procure trephine biopsy needles prioritize getting needles with calibrations as this will assist you as you perform the procedure as opposed to guessing based on prior experience which may be difficult when you are using uncalibrated needles. Also be gentle to avoid crushing the bone as you try to burrow-in.

Response: Dr. Simon Onsongo: it takes a lot of counselling to convince patients to consent a patient to have a bone marrow procedure because of the fear that they may have been exposed to before the procedure by other healthcare professionals therefore lets us not instill fear in patients that may not be proportional to the actual experience which in most of my patients has been comfortable and very acceptable.

Case 2

Question 1: what is the role of immunophenotyping: Immunohistochemistry (IHC) and flow cytometry in the diagnosis of myeloma?

Response: Dr. Valarie: immunophenotyping is the most definitive way to characterize your plasma cell population as clonal. Because of limited access or resources locally, we use serum protein electrophoresis which is more of a surrogate indicator because it is looking at what the plasma cells produce if it is producing a monoclonal protein. But the immunophenotype will definitively tell you these plasma cells are clonal based by surface cell markers. This also helps you to detect MRD status in terms of follow-up.

Question 2: what is the role of cytogenetics in the management of patients with multiple myeloma?

Response: Dr. Valarie: both for stratification in terms of management options and also for prognostication. Although this is not always possible in our setting because of cost so most of our patients receive standard therapy. But briefly cytogenetic testing enables us to identify patient with aggressive disease who may benefit from transplant and also gives prognostic information.

Response: Dr. Beatrice: immunohistochemistry (IHC) and flow cytometry could sometimes be confusing because in MM the plasma cells tend to reside more in the bone marrow than in peripheral blood therefore you may get a myeloma patient with negative flow cytometry results but positive for IHC. But both tests may prove to be useful when morphology is negative for myeloma because the cell surface markers will show myeloma cells if they are present.

Question 3: how often do you encounter young patients (<40 years) and what unique challenges do you face with these special group?

Response: Dr. Beatrice: not frequently but we have seen patients in 20s, 30s and 40s but this appears to be more common recently than before so we do not know whether these rates are rising. Young patients are still in the

reproductive age so that is a difficult scenario that you have to consider as you choose therapy. Stem cell transplant is also another consideration in that young patients tend to have less complications as compared to older patients

Response: Dr. Kelvin Manyega: the data that we have collected at Moi Teaching and Referral Hospital over the past 11 years shows that 15% of patients present at age <50 years which is unique because this corresponds with what has been observed in the African American population who have younger age at onset as compared to white patients.

Response: Dr. Simon Onsongo: the diagnosis is often missed in young patients because doctors often do not expect MM and therefore young patients tend to present very late when the disease has been progressed.