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Theragnostic Approach in Vascular malformations

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According to Classification of International Society for the Study of Vascular Anomalies (ISSVA) updated in 2014 and 2018, vascular anomalies are divided into two major groups of 'vascular tumours' and 'vascular malformations (VM)'. Vascular Malformations named according to its vessel involved, e.g. venous, capillary, arterial, lymphatic but also combined or syndromic. Most of them are sporadic ~90% and usually solitary and large, but some of them are hereditary, of which are usually multifocal and small in size. Genetic mutations occur in vascular endothelial cells during embryogenesis. Clinical variability exists in the same family as the double hit mechanism (inherited germline mutation 1st Allele plus somatic genetic defect of the same gene 2nd Allele to abolishes normal gene function) and this is the first step towards identification of etiopathogenesis and molecular pathways.

Molecular basis of the more common sporadic unifocal malformation is that genetic mutations within the tissue but not in blood samples as somatic changes only which could be confirmed by skin biopsy. In 2009, 50% sporadic VMs was found to have somatic activation mutation TIE2/TEK. In 2015, another 20% sporadic VMs was found to carry a somatic activation mutation PIK3CA. Hence, development of specific animal models may let to develop novel specific treatments. Multifocal sporadic VMs may have mosaic mutation then 2nd hit of variable somatic TIE2 mutation, while blue rubber bleb nevus has 2 somatic mutations on the same allele without 2nd hit that all lesions share the same mutation. Most vascular malformations are caused by mutations that activates one of the two major intracellular pathways: RAS/MAPK/ERK (proliferative) and PI3K/AKT/mTOR (anti-apoptosis) pathways. PIK3CA mutation not limited to 20% of venous malformation but also happened in lymphatic malformation (LM), PIK3CA-related overgrowth spectrum (PROS) and Klippel Trenaunay syndrome (KTS).

Interdisciplinary team approach in treatment of vascular anomalies includes a lot of specialists e.g. dermatologists, plastic surgeons, interventional radiologists and paediatricians. For the accurate diagnosis, only few complementary examinations are needed such as echo doppler, MRI,

arteriography and coagulation tests (e.g. D-dimer, fibrinogen) to propose an individualised treatment including medical, compression and interventional surgery, sclerosis and/or embolization. After our extensive insight into genetic and pathophysiologic origin of the abnormal signaling within vascular endothelial cells of different VMs, we can decide our targeted non-invasive medical treatments: i) sirolimus for symptomatic slow-flow VMs, LMs, capillary LMs, CLMs, KTS; ii) alpelisib (PIK3CA inhibitor) for PROS and iii) trametinib (MEK inhibitor.

Learning points:

- Vascular Malformations named according to its vessel involved, e.g. venous, capillary, arterial, lymphatic but also combined or syndromic.
- Clinical variability exists in the same family as the double hit mechanism with inherited germline mutation followed by somatic mutation.
- Through extensive insight into genetic and pathophysiologic origin of the abnormal signaling within vascular endothelial cells of different VMs, we can decide our targeted non-invasive medical treatments (sirolimus, alpelisib, trametinib) to different VMs.