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Editorial

Succinate dehydrogenase (SDH)–deficient neoplasia: An update

Banushree CS[1]*

[1] *Dept. of Pathology, Indira Gandhi Medical College and Research Institute, Puducherry, India*

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Succinate dehydrogenase (SDH) is a mitochondrial enzyme involved in the Krebs cycle and the electron transport chain. The enzyme complex has four subunits: SDHA, SDHB, SDHC, and SDHD. The flavoprotein-containing subunit SDHA and the iron sulfur-containing subunit SDHB act as catalytic cores. The SDHC and SDHD subunits act as a binding site for ubiquinone.[1,2] The loss-of-function mutations in any SDH gene or assembly factor (SDHAF2) lead to gastrointestinal stromal tumors (GIST), paragangliomas, renal cell carcinomas (RCC), and pituitary adenomas. The loss of SDH can also cause non-neoplastic lesions like neurometabolic disorders.[3,4] There are several known and unknown mechanisms by which loss of SDH causes cancer. The SDH is involved in suppressing metastasis and preventing angiogenesis. The succinate levels can increase in the absence of SDH and cause cancer.[5] The most common mutations seen in GIST are KIT and PDGFR-α . A small proportion (10%) of GIST is wild-type with SDH deficiency and comprises certain sporadic cases, pediatric GISTs, and syndromic association of Carney triad and Carney-stratakis syndrome.[6] It is very important to identify SDH-deficient GIST as it will not respond to imatinib.[7] The SDH-deficient GIST arises most commonly from the stomach, especially in young females. Grossly, present as multinodular and microscopically epithelioid morphology. Often with lympho-vascular invasion and metastasis. So, all gastric GIST should be screened for SDH subunits by immunohistochemistry. The commonest subunit deficient is SDHB followed by SDHA.[6] The SDH-deficient RCC is present at a wide age range and is usually multiple and bilateral often presenting with cystic change. Microscopically, Solid sheets of eosinophilic cells with occasional flocculent cytoplasmic inclusions. Among the four subunits, loss of SDHB is common in SDH-deficient RCC.[8]

Hereditary paraganglioma and Pheochromocytoma are associated with SDH and SDHAF2 mutations in 40% of cases. All the subunits of SDH can be mutated. The most aggressive mutation is of SDHB which can also be associated with RCC. The SDHA has low penetrance and SDHB has high penetrance. The SDHC is associated with Head and neck paragangliomas.[9] The SDHAF2 encodes a protein that integrates the FAD group into SDHA. Complete penetrance is seen in mutations associated with SDHAF2 mutation usually arising from parasympathetic ganglia.[10]

The SDH enzyme complex has multiple subunits. The mutations in any subunit can lead to various neoplasms and can have syndromic associations. Among them, SDHB mutation is the most common. Any patient below fifty years of age presenting with any SDH deficient tumor should be screened for tumors in another organ. The immunohistochemical stain of SDHB should be done initially followed by SDHA. The diagnosis of SDH deficient tumor is crucial for personalized therapy and follow-up.

* *Corresponding author*.
E-mail address: drbanushree15@hotmail.com (Banushree CS).

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2. Conflict of Interest

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Author's biography

Banushree CS, Professor & Head https://orcid.org/0000-0003-4637-8837

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