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Carney Complex

Carney Complex is a rare inherited genetic disorder classified under the multiple endocrine neoplasia syndromes. It is characterized by a distinct combination of pigmented skin and mucosal lesions, as well as an array of both endocrine and non-endocrine tumors. Historically referred to as NAME syndrome (Nevi, Atrial Myxoma, Ephelides) and LAMB syndrome (Lentigines, Atrial Myxoma, Blue Nevi), Carney Complex should be distinguished from Carney Triad, a separate condition marked by paragangliomas, gastric stromal tumors, and pulmonary chondromas.

Epidemiology and Genetics

Carney Complex is exceedingly rare, with fewer than 750 documented cases worldwide. The syndrome primarily follows an autosomal dominant inheritance pattern, although approximately 25% of cases are sporadic. The disease exhibits high penetrance, meaning that it manifests in most individuals who inherit the gene mutation, but it shows variable expressivity, with clinical features varying significantly among affected individuals.

The majority of Carney Complex cases are associated with inactivating mutations in the PRKAR1A gene located on chromosome 17q22-24. This gene encodes a regulatory subunit of protein kinase A , which is involved in various cellular processes, including endocrine hormone regulation. A secondary locus on chromosome 2p16 has also been implicated in some cases.

Clinical Manifestations

Carney Complex manifests with a wide spectrum of clinical features, including both cutaneous and systemic tumors. The hallmark of Carney Complex is the presence of distinctive pigmented lesions. Common types include:

- ***Lentigines***: These well-defined, small (typically <5 mm) pigmented macules appear in varying shades of tan, brown, or black and are found on the skin and mucosal surfaces. Lentigines are present in 70-80% of patients and are the most recognizable feature.
- ***Blue Nevi***: These are dark blue or gray papules that are intensely pigmented.
- ***Other Pigmented Lesions***: These include café-au-lait macules, nevus spilus, and Spitz nevi, which can be found in affected individuals.

Endocrine Tumors

Carney Complex is associated with several endocrine tumors, which often have distinctive clinical presentations:

- ***Primary Pigmented Nodular Adrenocortical Disease***: This condition involves ACTH-independent cortisol production, which results in Cushing syndrome. It is a significant cause of morbidity in affected individuals.
- ***Growth Hormone Hypersecretion***: In some cases, affected individuals may develop asymptomatic growth hormone hypersecretion, with acromegaly potentially occurring in 10-15% of cases.
- ***Large Cell Calcifying Sertoli Cell Tumor***: A testicular tumor that can lead to gynecomastia or precocious puberty in males.
- ***Thyroid Involvement***: Thyroid nodules or even thyroid carcinoma can develop in some patients.
- ***Ovarian Tumors***: Though rare, women with Carney Complex may experience ovarian cysts, serous cystadenomas, teratomas, or endometrioid carcinoma.

Non-Endocrine Tumors

In addition to endocrine tumors, Carney Complex is associated with a range of non-endocrine tumors:

- ***Cardiac Myxomas***: These benign heart tumors often develop at a younger age compared to sporadic myxomas and can occur simultaneously in multiple chambers of the heart.
- ***Psammomatous Melanotic Schwannomas***: These can arise within the central or peripheral nervous system, particularly in the gastrointestinal tract and along spinal nerve roots.
- ***Benign Breast Tumors:*** Frequently seen in women, these tumors are often misdiagnosed as fibrocystic changes.

Diagnosis

The diagnosis of Carney Complex is primarily clinical and can be confirmed through genetic testing. Major Diagnostic Criteria include:

- Spotty skin pigmentation (typically located on lips, conjunctiva, and mucosal surfaces)
- Myxomas (cutaneous, mucosal, and cardiac)
- Primary pigmented nodular adrenocortical disease or altered cortisol excretion following dexamethasone administration
- Acromegaly due to growth hormone-producing adenomas
- Large cell calcifying sertoli cell tumor or characteristic calcifications on testicular ultrasound
- Psammomatous melanotic schwannomas

Diagnosis can be further supported by identifying a pathogenic variant in the PRKAR1A gene or the presence of one major diagnostic criterion with a family history of Carney Complex or a confirmed PRKAR1A mutation.

Differential Diagnosis

Several other syndromes may present with overlapping features, making differential diagnosis essential:

- ***Peutz-Jeghers Syndrome (PJS)*:** PJS is marked by pigmentation on the lip mucosa and gastrointestinal polyposis but lacks the myxomas and blue nevi characteristic of Carney Complex.
- ***LEOPARD Syndrome*:** This syndrome presents with lentigines and specific cardiac abnormalities but does not involve myxomas.
- ***PTEN Hamartoma Tumor Syndromes***: Including Cowden disease, these syndromes are characterized by hamartomas and lentigines, but they do not present with the characteristic myxomas of Carney Complex.
- ***McCune-Albright Syndrome*:** Defined by polyostotic fibrous dysplasia, café-au-lait macules, and precocious puberty, McCune-Albright syndrome does not involve the same cutaneous and mucosal lesions seen in Carney Complex.
- ***Benign Familial Lentiginosis*:** This condition is marked by lentigines that spare mucosal surfaces and lack the systemic abnormalities seen in Carney Complex.

Management and Surveillance

Management of Carney Complex involves regular monitoring to assess for the development of endocrine and non-endocrine tumors. While formal surveillance guidelines are not established, the following measures are commonly recommended:

- Annual EKG: To monitor for cardiac myxomas.
- Annual Thyroid Ultrasound: To detect thyroid nodules or cancer early.
- Annual Testicular Ultrasound: For boys before puberty, to monitor for Sertoli cell tumors.
- Annual 24-hour Urinary Free Cortisol Measurement: To assess adrenal function and detect Cushing syndrome.
- Annual Measurement of Insulin-like Growth Factor-1 (IGF-1) and Prolactin: To monitor for growth hormone abnormalities.
- Transabdominal Ultrasound: For women to monitor for ovarian tumors.

Conclusion

Carney Complex is a rare and complex disorder with significant clinical implications. Due to its diverse presentation, which includes both endocrine and non-endocrine tumors, early diagnosis

and vigilant long-term surveillance are essential for optimizing patient outcomes. Continued advancements in genetic testing and an improved understanding of the underlying mechanisms of the syndrome may lead to more targeted and effective therapeutic approaches in the future.

References

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