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Neuroendocrine Biomarkers

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ABSTRACT

Neuroendocrine cells are unique because they are found in almost every organ in the body. These cells often resemble other cell types, making it challenging to differentiate them based on histological imaging. In the case of neuroendocrine tumors, which can also occur in nearly all organs, neuroendocrine biomarkers are commonly utilized for diagnosis. Neuroendocrine biomarkers are classified into two categories, serum biomarkers and tissue biomarkers. The most commonly used neuroendocrine biomarkers in clinical practice are Synaptophysin, Chromogranin A, and CD56. These biomarkers are typically assessed in neuroendocrine tissue through immunohistochemistry testing, often used in combination to enhance diagnostic accuracy. Other tissue-detectable biomarkers include INSM1, S100, and Inhibin. Additionally, certain biomarkers, such as Neuron-Specific Enolase (NSE) and Serotonin, are predominantly utilized for diagnosing neuroendocrine tumors through serum analysis. This literature review aims to explore neuroendocrine biomarkers detected in serum and tissue, emphasizing their role in diagnosing neuroendocrine tumors.

Keywords: neuroendocrine cancer; tissue biomarker; chromogranin; synaptophysin; CD56.

INTRODUCTION

Neuroendocrine cells are found throughout the body and are integral to the neuroendocrine system [1]. These cells possess characteristics of both nervous and endocrine cells, enabling them to produce and release hormones, often peptides, into surrounding tissues or the bloodstream [1, 2]. Neuroendocrine cells play crucial roles in various bodily functions, including metabolism, stress response, growth, and reproduction [2]. However, due to genetic mutations, neuroendocrine cells may undergo rapid proliferation, resulting in the development of neuroendocrine tumors (NETs) [4].

NETs are a type of tumor that can arise in various organs, given the widespread distribution of neuroendocrine cells throughout the body [3]. These tumors are most commonly located in the gastrointestinal tract and lungs [3]. Because neuroendocrine cells naturally produce hormones, patients with neuroendocrine tumors may experience excessive hormone production, often leading to paraneoplastic syndromes, commonly referred to as functional tumors [3]. In contrast, the majority of cases involve non-functional tumors, where patients do not exhibit specific symptoms [5]. Thus, diagnosing neuroendocrine tumors cannot rely solely on clinical symptoms. Moreover, since neuroendocrine cells frequently share similar histological features with other cell types, their diagnosis necessitates more specific tools, such as neuroendocrine biomarkers.

REVIEW CONTENT

Biomarkers in NETs are broadly categorized into two types: serum and tissue biomarkers [5]. Some biomarkers are exclusively detectable in serum or tissue, while others can be identified in both. Additionally, not all biomarkers are directly utilized for diagnosing NETs; some are used in clinical settings to differentiate NETs from other tumor types. This review aims to identify various neuroendocrine biomarkers found in serum and tissues and explore their potential as diagnostic tools for neuroendocrine tumors.

1. Synaptophysin

Synaptophysin is a biomarker with high sensitivity but limited specificity, making it one of the most widely used tissue markers, particularly for neuroendocrine tumors (NETs) [6]. This transmembrane protein, located in the synaptic vesicles of neuroendocrine cells, serves as a reliable indicator for identifying neuroendocrine tumors [7]. However, the expression of Synaptophysin varies between low-grade and high-grade neuroendocrine tumors, influenced by metabolic changes and the secretory activity of neuroendocrine cells. Studies have reported that the specificity and sensitivity of Synaptophysin are both above 90% [9]. In addition to its expression in neuroendocrine tumors, Synaptophysin is also found in various other organs and cell types throughout the body. It is expressed in the cerebrum, cerebellum, the islets of Langerhans in the pancreas, as well as in axons and ganglion cells

within the peripheral nerves located in the walls of the gastrointestinal tract [8]. This widespread distribution contributes to Synaptophysin's low specificity in diagnosing neuroendocrine tumors. To enhance diagnostic accuracy, it is essential to use Synaptophysin alongside other biomarkers, such as Chromogranin A and CD56, as part of a comprehensive biomarker panel for neuroendocrine tumor evaluation.

2. Chromogranin A

Chromogranin A is a protein located within the secretory vesicles of neuroendocrine cells, where it functions to store hormones, neurotransmitters, peptides, and growth factors until they are released into circulation in response to nervous system signals [10]. Chromogranin A is one of the most commonly used biomarkers, alongside Synaptophysin. While it exhibits higher specificity compared to Synaptophysin, its sensitivity is relatively lower [6]. Chromogranin A can be assessed both in tissue samples and in serum. In tissue, Chromogranin A is often utilized as a diagnostic tool for identifying neuroendocrine differentiation through immunohistochemistry (IHC). This approach is particularly valuable for diagnosing localized neuroendocrine tumors, such as those in the gastrointestinal tract (GEP-NETs) or lungs (Lung NETs). In these cases, Chromogranin A is frequently combined with other biomarkers to enhance the accuracy of the immunohistochemical evaluation. In contrast, serum Chromogranin A testing is primarily used to monitor disease progression and recurrence, assess tumor burden, and evaluate response to treatment. However, Chromogranin A is not classified as a highly specific tissue marker because its levels can also be elevated in several non-neuroendocrine conditions. These include chronic atrophic gastritis, renal and hepatic dysfunction, cardiovascular diseases, and certain rheumatologic conditions [11]. Therefore, while it is a valuable biomarker in neuroendocrine tumor diagnosis and management, its interpretation must be contextualized within the broader clinical picture.

3. CD56

CD56, also known as neural cell adhesion molecule (NCAM), is a glycoprotein predominantly expressed on the surface of neurons, natural killer (NK) cells, and various neuroendocrine cells. It plays a critical role in cell adhesion, migration, and signaling, which makes it a valuable biomarker for identifying neuroendocrine tumors (NETs) in diagnostic pathology. The expression of CD56 is considered a hallmark of many neuroendocrine tumors, and studies have reported that it has high sensitivity, but limited specificity, meaning it is effective at detecting NETs but can also be found in other malignancies. To diagnose neuroendocrine tumors, immunohistochemical staining is typically used, as CD56 serves as a key tissue marker for neuroendocrine cells. CD56 exhibits broad sensitivity across various types of NETs, with studies showing expression rates exceeding 90% in certain NET subtypes. However, CD56 is not entirely specific to NETs—it is also commonly expressed in certain hematological malignancies, such as NK-cell lymphoma, as well as in other neoplasms, such as small-cell lung carcinoma. This broad expression across different malignancies explains why CD56, while useful, may also support the diagnosis of non-neuroendocrine cancers, highlighting the importance of using it in conjunction with other markers for a more accurate diagnosis [12].

4. S100

S100 is a type of calcium-binding protein that is specifically expressed in vertebrate cells [18]. This protein is involved in various cellular pathways and plays a crucial role in processes such as proliferation, apoptosis, differentiation, and inflammation. While S100 is not a tissue-specific biomarker for neuroendocrine tumors, it can detect a wide range of malignancies, including melanoma, schwannomas, and various types of carcinomas. The specificity and sensitivity of S100 for neuroendocrine tumors range from 30-60% and 50-70%[19]. In neuroendocrine tissue testing, S100 is used as a biomarker through immunohistochemical examination. This method is particularly useful for identifying mixed tumors, where both neuroendocrine and neuroectodermal components are present, such as in gangliogliomas, which consist of both ganglion cells and glial cells. However, S100 is not specific to neuroendocrine tumors, as it is also expressed in neuroectodermal cells and mesenchymal tissue. Therefore, to accurately diagnose neuroendocrine differentiation, S100 should be used alongside other more specific neuroendocrine biomarkers, such as Chromogranin A, Synaptophysin, or CD56. By combining these markers, clinicians can obtain a more precise and reliable diagnosis for neuroendocrine tumors[17].

5. NSE

Neuron-Specific Enolase (NSE) is a glycolytic enzyme that plays a critical role in glucose metabolism within cells. It is predominantly found in the cytoplasm of neurons and neuroendocrine cells. NSE is predominantly used as a serum biomarker. In this capacity, NSE is mainly employed to monitor disease progression, tumor burden, and treatment response in patients with neuroendocrine tumors (NETs). NSE has moderate sensitivity and specificity for neuroendocrine tumors, though its specificity is somewhat limited. Elevated levels of NSE can also occur in other conditions, such as brain injuries, which may interfere with its use as a definitive diagnostic tool. Despite these limitations, NSE remains a useful biomarker in blood tests to assess disease progression and monitor treatment efficacy in patients with neuroendocrine tumors. When used as a tissue biomarker, NSE can help differentiate neuroendocrine tumors from other types of tumors. For example, adenocarcinomas, renal cell carcinomas, melanomas, and lymphomas typically do not express NSE, making it a valuable tool in distinguishing neuroendocrine tumors from these other malignancies [20].

6. INSM1

INSM1 is a protein that serves as a key transcription factor in the differentiation of neuroendocrine cells

during embryonic development [13,14]. Recently, INSM1 has emerged as one of the newest and most valuable tissue biomarkers for neuroendocrine tumors (NETs). It is frequently used in combination with other markers to assess neuroendocrine differentiation through immunohistochemistry testing. Its high sensitivity and specificity make it particularly useful for confirming the diagnosis of both primary and metastatic neuroendocrine tumors when combined with other biomarkers [13,15,16]. Moreover, INSM1 can complement other biomarkers by helping differentiate between neuroendocrine tumors and non-neuroendocrine tumors. For instance, adenocarcinomas typically show little to no expression of INSM1 [15]. Several studies have demonstrated that INSM1's specificity for neuroendocrine differentiation ranges from 71-100%. A key distinction between INSM1 and other commonly used markers, such as Synaptophysin and Chromogranin A, is that while Synaptophysin is expressed in adrenocortical neoplasms and Chromogranin A can also be found in basal cell carcinoma of the skin, INSM1 is not expressed in non-neuroendocrine tumors, making it a more reliable and specific biomarker compared to the other two [14].

7. Pancreatic Polypeptide (PP)

Pancreatic Polypeptide (PP) is a polypeptide produced by cells in the pancreas that plays a role in regulating pancreatic secretion, as well as affecting liver glycogen storage and gastrointestinal secretion. Pancreatic polypeptide is primarily used as a serum biomarker for detecting neuroendocrine tumors (NETs), particularly pancreatic neuroendocrine tumors (PanNETs). Similar to other serum biomarkers, an increase in Pancreatic Polypeptide levels in blood tests can indicate disease progression, tumor size, and treatment response in patients with neuroendocrine tumors. Although less commonly, pancreatic polypeptide can also be used as a tissue biomarker to confirm neuroendocrine differentiation, especially in tumors originating from the pancreas and gastrointestinal tract. However, its use as a tissue biomarker is less frequent when compared to more widely used markers like Synaptophysin and Chromogranin A. The sensitivity of PP for neuroendocrine tumors typically ranges between 40-80%, while its specificity ranges from 60-90%. Despite its usefulness in identifying pancreatic neuroendocrine tumors, Pancreatic Polypeptide is not entirely specific, as its expression can also be elevated in non-neuroendocrine tumors, which limits its diagnostic precision [25,26].

8. GFAP

Glial Fibrillary Acidic Protein (GFAP) is a well-known intermediate filament protein primarily associated with astrocytes, a type of glial cell in the central nervous system (CNS). While GFAP is most commonly used to identify astrocytes in the brain and spinal cord, its utility as a neuroendocrine biomarker arises from its presence in glial-like or supporting cells in neuroendocrine tissues and related pathological conditions.

GFAP is not typically expressed in neuroendocrine cells themselves, but it may be detected in glial components or mixed tumors where neuroendocrine tumors contain a glial component. For instance, in gangliogliomas, which are mixed neuroendocrine-glial tumors, GFAP expression can be present in the glial component of the tumor, helping to distinguish these from purely neuroendocrine neoplasms. However, GFAP is not a direct marker for neuroendocrine cells or their activities. Thus, it must be used in conjunction with other neuroendocrine markers such as Chromogranin A, Synaptophysin, or neuron-specific enolase (NSE) to accurately interpret tissue samples and provide a reliable diagnosis [27,28].

9. Human Chorionic Gonadotropin (HCG)

Human Chorionic Gonadotropin (HCG) is a glycoprotein hormone typically produced by the placenta during pregnancy, but it is also found in certain types of tumors, including neuroendocrine tumors. As a biomarker, HCG can be assessed both in serum and tissue. When used as a tissue biomarker, HCG is helpful for assessing neuroendocrine differentiation in tumors such as choriocarcinomas, germ cell tumors, and some neuroendocrine tumors that express HCG. This examination is valuable for confirming histological features and distinguishing HCG-producing tumors from those that do not secrete the hormone. Additionally, immunohistochemical staining can differentiate between primary tumors and metastatic tumors, particularly in cases of germ cell tumors expressing HCG. As a serum biomarker, HCG is primarily used to monitor disease progression, tumor size, and treatment response. It provides important information for tracking the course of the disease in patients with HCG-producing tumors. However, the sensitivity and specificity of HCG as a biomarker for neuroendocrine tumors can vary depending on whether it is tested in serum or tissue and the specific type of tumor being evaluated [29].

10. Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) can serve as a valuable serum biomarker for neuroendocrine tumors (NETs), particularly carcinoid tumors, which secrete Serotonin and its metabolites. Carcinoid tumors are neuroendocrine tumors that usually appear on the gastrointestinal tract, lung, or possibly liver. Carcinoid tumors are usually considered not aggressive but can cause hormonal imbalances and lead to several health issues. Elevated serum Serotonin levels are often an indicator of these tumors, as they produce and release Serotonin into the bloodstream. High Serotonin levels are often associated with carcinoid syndrome, which can cause symptoms such as flushing, diarrhea, and wheezing, or what we usually call paraneoplastic syndromes. Furthermore, measuring Serotonin in the serum allows for non-invasive monitoring of treatment response, as a decrease in Serotonin levels may indicate that the tumor is responding to therapy. However, while serum Serotonin is useful, it is not entirely specific to NETs and can be influenced by other conditions, which is why it is typically used

alongside other biomarkers for a more accurate diagnosis [30,31].

11. Gastrointestinal Hormone

Glucagon, Gastrin, Vasoactive Intestinal Peptide (VIP), and somatostatin are hormones produced by neuroendocrine cells and serve as important serum and tissue biomarkers for mainly gastrointestinal neuroendocrine tumors. As serum biomarkers, elevated levels of Glucagon can indicate the presence of glucagonoma, a rare pancreatic neuroendocrine tumor that leads to hyperglycemia and dermatitis. Similarly, high Gastrin levels are associated with gastrinoma, commonly found in the duodenum or pancreas, and can cause Zollinger-Ellison syndrome, characterized by gastric acid hypersecretion and ulcers. Elevated VIP levels are seen in VIPomas, which present with watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome), and are particularly useful for monitoring disease progression in VIPoma patients. Somatostatin, when elevated in the serum, may indicate somatostatinoma, a tumor of the pancreas or gastrointestinal tract that leads to symptoms like gallstones and diabetes. As tissue biomarkers, Glucagon, Gastrin, VIP, and Somatostatin are expressed in specific neuroendocrine cells, such as alpha cells of the pancreas for Glucagon, G cells in the stomach for Gastrin, and D cells in the pancreas and gastrointestinal tract for somatostatin [23,24].

12. Inhibin

Inhibin is a glycoprotein hormone primarily produced by the gonads (testes and ovaries), adrenal glands, and placenta. It plays a key role in regulating the hypothalamic-pituitary-gonadal (HPG) axis by selectively inhibiting the secretion of follicle-stimulating hormone (FSH) from the anterior pituitary [22]. While Inhibin is not classically considered a neuroendocrine hormone, its production and regulation have implications in neuroendocrine signaling and pathology. As a biomarker, Inhibin is primarily used in the diagnosis and monitoring of certain neuroendocrine and endocrine neoplasms. Inhibin is most commonly used as a serum biomarker to evaluate tumor burden and treatment response in gonadal tumors (such as granulosa cell tumors of the ovary and Sertoli-Leydig cell tumors of the testis), adrenal cortical tumors, and some pituitary adenomas. Elevated levels of Inhibin in the serum may indicate the presence of these tumors. As a tissue biomarker, Inhibin is commonly assessed through immunohistochemical staining to help identify gonadal or adrenal tumors with neuroendocrine features. This is particularly useful for differentiating gonadal tumors from other types of neuroendocrine tumors and endocrine-related neoplasms. Inhibin expression in tissues can help confirm tumors of gonadal or adrenal origin, as these neoplasms often share overlapping characteristics with neuroendocrine tissue [21].

CONCLUSION

Neuroendocrine biomarkers used as a tool to diagnose neuroendocrine tumors through tissue or serum detection. The most often used neuroendocrine biomarkers are Chromogranin A, Synaptophysin, CD56, and S100, due to their reliability in identifying neuroendocrine tissues. Additionally, INSM1 has emerged as a valuable tissue biomarker, offering enhanced specificity for neuroendocrine cells. In serum, NSE is commonly used, while Serotonin and gastrointestinal hormones aid in subtype identification. Additionally, biomarkers like Pancreatic Polypeptide, GFAP, Inhibin, and HCG help differentiate neuroendocrine tumors from other tumor types. Combining these biomarkers enhances diagnostic accuracy and tumor classification.

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