VIP-Secreting Composite Pheochromocytoma-ganglioneuroblastoma

VIP-Secreting Composite Pheochromocytoma

Pheochromocytoma

- Chromaffin cell tumor, usually arise in the adrenal medulla
- Can secrete hormones other than catecholamines including EPO, calcitonin, PTHrP, ANP, renin, ACE, serotonin, gastrin, somatostatin, and **VIP**

VIP-secreting tumors

- Pancreatic tumors: pancreatic islet cells
- Extrapancreatic tumors: ganglioneuroblastoma, ganglioneuroma, neurofibroma, pheochromocytoma, bronchogenic carcinoma, medullary thyroid carcinoma

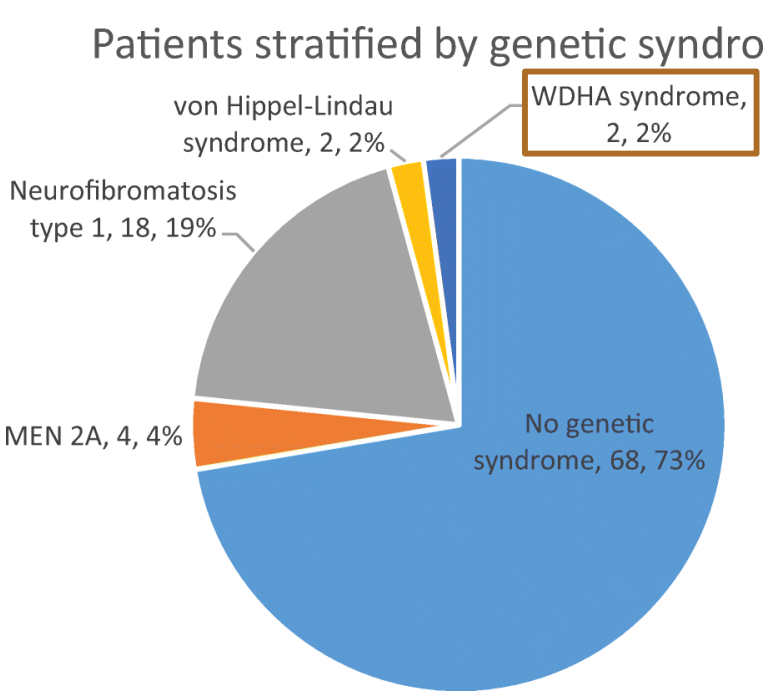
Composite pheochromocytoma

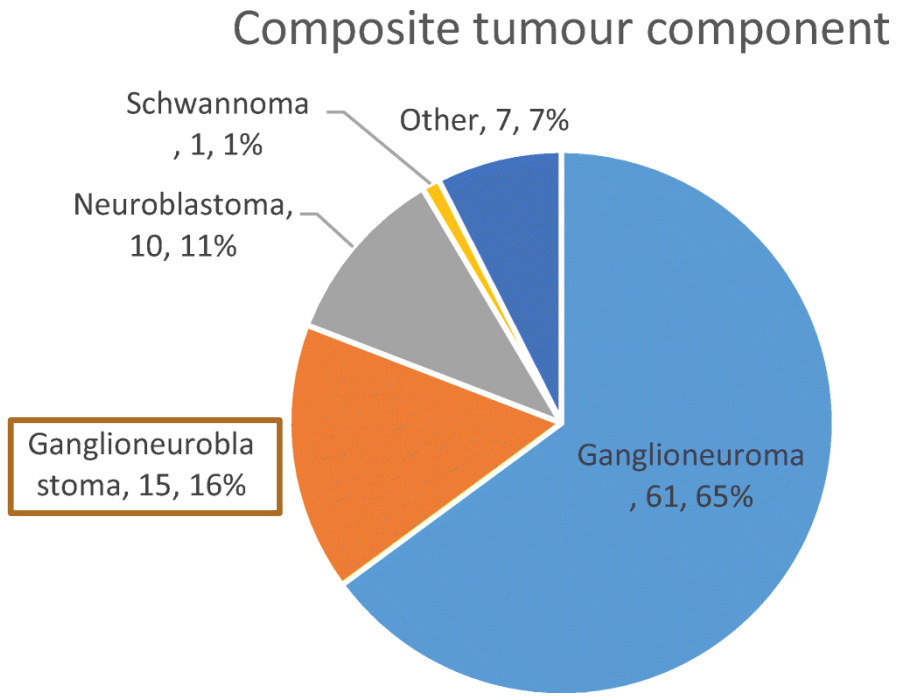
- Rare
- Co-exist with another type of tumor, usually the same embryological origin (i.e. Neural crest)
  - Ganglioneuroma, schwannoma, ganglioneuroblastoma, malignant peripheral nerve sheath tumor, neuroendocrine carcinoma

K. Dhanasekar et al. *Langenbeck's Archives of Surgery* (2022) 407:517–527
Shida et al. *BMC Res Notes* (2015) 8:257
Shelby K.Y. et al. *AACE Clinical Case Rep. 8* (2022) 158e162

Composite Pheochromocytoma

- Affect men and women equally (Male 42%, Female 54%)
- Occurring between the third and fifth decades: Median age 48 years, (Range 4-86 years)

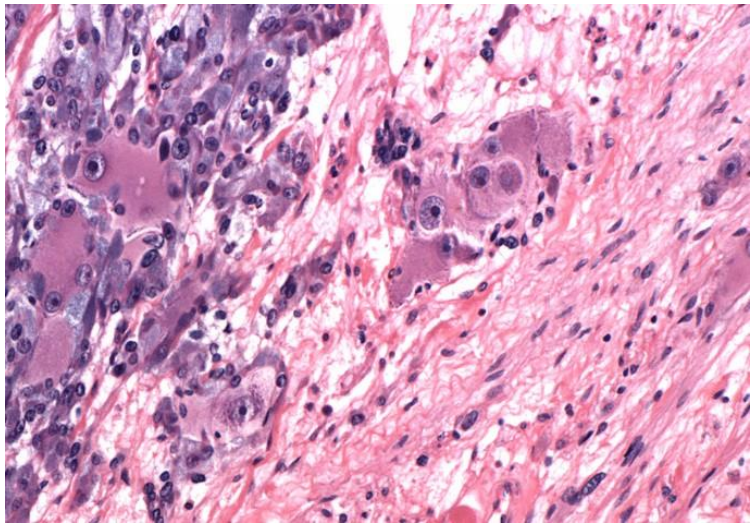


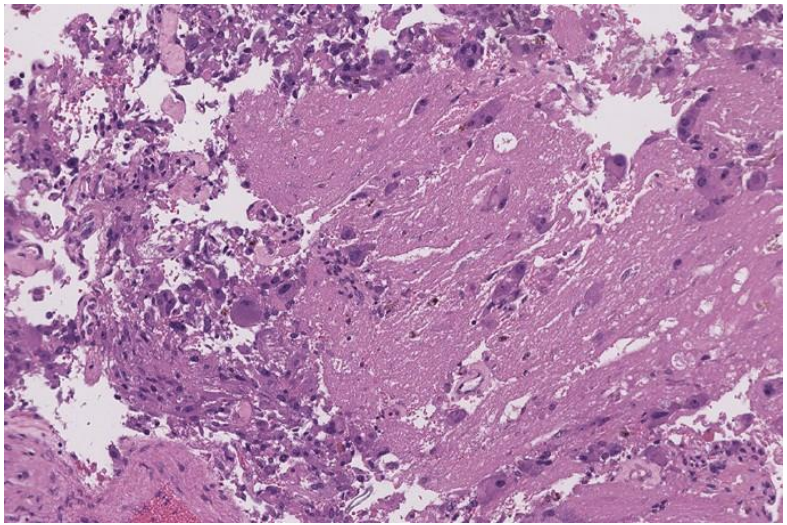


K. Dhanasekar et al. *Langenbeck's Archives of Surgery* (2022) 407:517–527

Composite Pheochromocytoma

- The composite elements are diagnosed using universal morphologic and/or immunohistochemical criteria





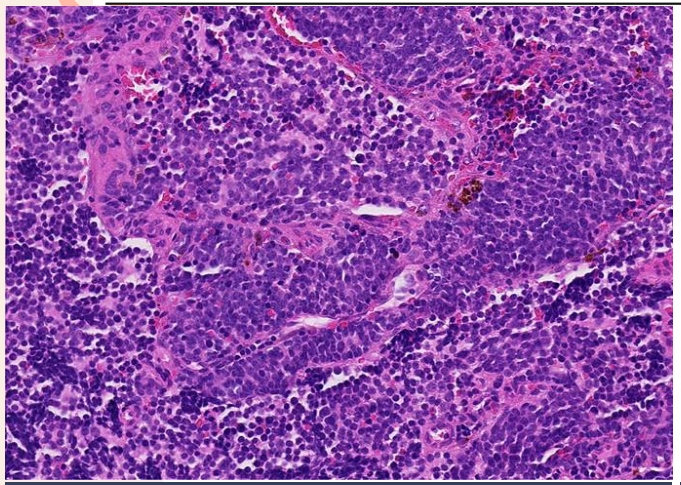
- It is suggested that at least 5% of the tumor should be composed of each tumor type, emphasizing the need for adequate tumor sampling
- Prognosis is often dependent on the highest grade component present

Endocrine Pathology (2022) 33:90–114

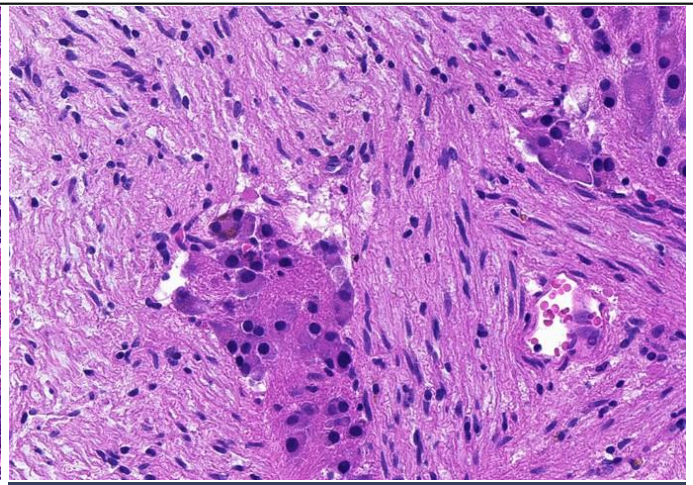
Composite Pheochromocytoma

Table 1 International Neuroblastoma Pathology Committee classification of neuroblastic tumors

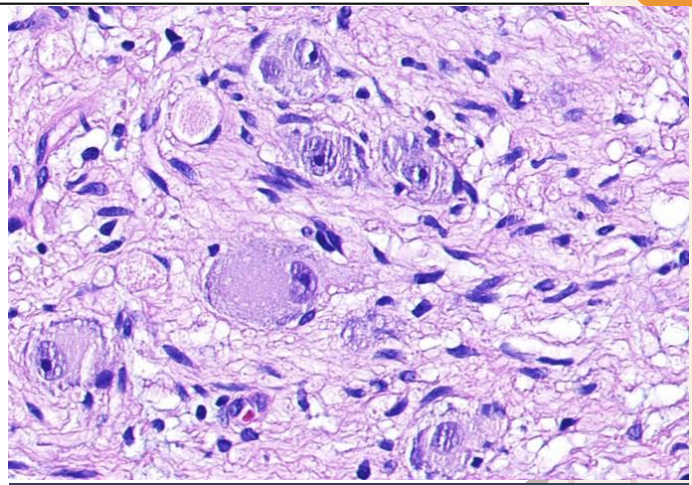
Diagnostic category	Subtype	Morphological characteristics
Neuroblastoma	*Undifferentiated*	Small blue round cells
	Poorly differentiated	Neuroblasts and neuropil; less than 5% ganglion cell differentiation
	Differentiating	Neuroblasts and neuropil; more than 5% ganglion cell differentiation
Ganglioneuroblastoma	*Intermixed*	More than 50% Schwannian stroma; at least one focus of neuroblasts
	Nodular	More than 50% Schwannian stroma; one dominant nodule composed of neuroblasts
Ganglioneuroma	*Maturing*	No foci of neuroblasts; some ganglion cells are not mature
	Mature	No foci of neuroblasts; all ganglion cells are mature



Neuroblastoma



Ganglioneuroblastoma



Ganglioneuroma

Endocrine Pathology (2022) 33:90–114

Composite Pheochromocytoma

- Identification of composite pheochromocytoma may also be a harbinger of some inherited pheochromocytoma including MEN2, MEN5, and NF1 syndromes

- Composite tumors do not appear to be a feature of the SDHx mutation-related syndromes

VIP-Secreting Composite Pheochromocytoma

Clinical Manifestations:

- **Excessive of VIP: WDHA syndrome**
  - Profound secretory diarrhea (often ≥3 L/day) 54.5%
  - Electrolyte abnormalities 45.6%
    Hypomagnesemia/hypokalemia
  - Hypochlorhydria/achlorhydria 42.4%
  - Other possible features
    Hypotension from vasodilation
    Hyperglycemia (20%-50%)
    Hypercalcemia (25%-50%)
- Symptoms of excess catecholamines

Vasoactive intestinal peptide (VIP)
28-amino-acid polypeptide neurohormone

Adheres to receptors on intestinal epithelial cells

↓

Activation of adenylate cyclase and cAMP production

↓

Excretion and suppresses the reabsorption of Na, Cl, K, water in the intestine

↓

Profound secretory diarrhea

- VIP also displays vasomotor action on vessels, glucogenolytic effect on liver and reduces gastric acid secretion

- **Vasodilatory effects of VIP "masked" the hypertensive effects of catecholamines**

Abdullayeva L. *World Acad Sci J* 1: 229-235, 2019
Shelby K.Y. et al. *AACE Clinical Case Rep. 8* (2022) 158e162

VIP-secreting Pheochromocytoma

Author, y	Age/ sex	Baseline hypertension	Case presentation	Tumor size, characteristics	Metastatic disease		
Hermel et al[5], 2021	30F	N	Hypertension, tachycardia, headache, anxiety	11 cm	N	Octreotide, metyrosine, embolization, surgical resection	Complete resolution of symptoms, normalization of laboratory values
Negro et al[6], 2021	71M	N	WDHA syndrome	10 cm, PASS of 20	Y, metastatic at presentation	Surgical resection of primary tumor, octreotide, sunitinib for recurrence	Recurrence, death 3 mo after resection
Hu et al[7], 2018	53F	N	Hypertension, seizure, followed by shock, flushing, WDHA syndrome	7 cm	N	Octreotide, surgical resection	Complete resolution of symptoms, normalization of laboratory values
Jiang et al[8], 2014	45M	N	WDHA syndrome	9 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
			WDHA syndrome with progression	Not reported	Y	Octreotide, radiation, surgical resection of primary tumor, sunitinib	Metastatic disease 3 y after resection with elevated VIP levels and WDHA syndrome responsive to sunitinib
Kikuchi et al[10], 2012	12F	N	, WDHA syndrome	8.0 cm	Y	Surgical resection of primary tumor	Lung/liver metastases, 3 y after resection WDHA syndrome, 13 y after resection Death, 14 y after resection
			WDHA syndrome, sweating, palpitations	12 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
Ikuta et al[12], 2007	49F	N	WDHA syndrome	7 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
Smith et al[13], 2002	78F	Y	WDHA syndrome	6 cm	N	Octreotide, surgical resection	Complete resolution of symptoms, normalization of laboratory values
Nigawara et al[14], 1987	43M	Unknown	WDHA syndrome	11 cm	Y	Surgical resection	Surgical resection of primary tumor, embolization of metastases
			WDHA syndrome	8.5 cm	N	Surgical resection	
			WDHA syndrome	5 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
Matta et al[17], 1978	43F	Unknown	WDHA syndrome	15 cm	N	Surgical Resection	
Loehry et al[4], 1975	28F	Unknown	WDHA syndrome, headaches, palpitations, hypertension	Not reported	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values

Composite Pheochromocytoma

Composite PHEO-Ganglioneuroma

Composite PHEO-Ganglioneuroblastoma

Shelby K.Y. et al. *AACE Clinical Case Rep. 8* (2022) 158e162

VIP-secreting Composite Pheochromocytoma

Reference	Age (y) and sex	Symptoms and signs	Primary adrenal gland site	Tumor size (cm)	Pathologic findings	Recurrent/ metastatic tumors	Prognosis	Family history
George et al (3)	21 F	Diarrhea, weight loss	Right	16	Pheochromocytoma/ ganglioneuroma	None	Alive	None
Nigawara et al (4)	28 M	Diarrhea	Right	250 g	Pheochromocytoma/ ganglioneuroblastoma	Invasion to inferior vena cava and bile duct. Local recurrence (37 yo). Metastasis to liver	Died of myocardial infarction (43 yo)	ND
Trump et al (5)	40 F	Diarrhea, weight loss	Left	15	Pheochromocytoma/ ganglioneuroma	None	Alive	ND
Onozawa et al (6)	47 F	Diarrhea, weight loss, hypertension	Left	13	Pheochromocytoma/ ganglioneuroma	None	Alive	NF1
Mahajan et al (7)	49 F	Diarrhea, headache	Right	6	Pheochromocytoma/ ganglioneuroma	None	Alive	None
Ishiguro et al (8)	51 M	Diarrhea, flushing, periodic paralysis	Right	7.4	Pheochromocytoma/ ganglioneuroma	None	Alive	None
Layfield et al (9)	51 F	Diarrhea, hypokalemia	Right	14	Pheochromocytoma/ ganglioneuroma	None	Alive	ND
Contreras et al (10)	61 M	Diarrhea, flushing, hypertension	Right	5.9	Pheochromocytoma/ ganglioneuroma	None	ND	ND
Salmi et al (11)	65 F	Diarrhea, weight loss	Right	13	Pheochromocytoma/ ganglioneuroma	None	ND	ND
Current case	26 F	Diarrhea, weight loss, hypokalemia	Right	8	Pheochromocytoma (primary, 12 yo). Pheochromocytoma/ ganglioneuroma (autopsy)	Metastasis to lung and liver (15 yo), lymph nodes, bone	Died (26 yo)	None

KiKuchi Y. et al. *Endocr Pract*.2012;18(No.4)

A Case of Recurrent Malignant Pheochromocytoma Complicated by Watery Diarrhea, Hypokalemia, Achlorhydria Syndrome

KAZUO NIGAWARA, TADASHI SUZUKI, HIROTSUGU TAZAWA, TOMIHISA FUNYU, SOROKU YAGIHASHI, KANEMITSU YAMAYA, YURIKO TERAYAMA, AND KEN YAMAGUCHI

Serum K	2.3 mmol/L	
Plasma NE	21.6 nmol/L	(0.30-1.77)
Plasma E	4250 pmol /L	(65-1299)
Plasma DA	1570 pmol/L	(65-1299)
Plasma VIP	7200 ng/dL	(0-100)

A 43-year-old Japanese man

1963

- Diarrhea, weakness, hypokalemia
- Dx Rt pheochromocytoma s/p Rt adrenalectomy
- Patho: Pheochromocytoma-ganglioneuroma

1982

- Intractable diarrhea, hypokalemia
- Dx Rt recurrent pheochromocytoma with liver metastasis
- Rx Common hepatic artery chemoembolization → MI Death
- Patho: **Pheochromocytoma-ganglioneuroblastoma** (well-differentiated)

Nihawara K. et al. *J Clin Endocrinol Metab* 65: 1053, 1987

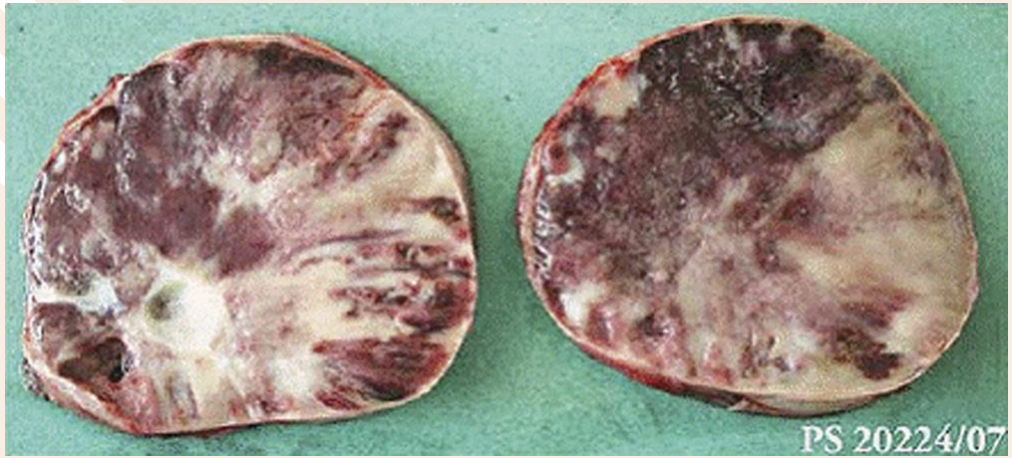
VIP-secreting Composite Pheochromocytoma

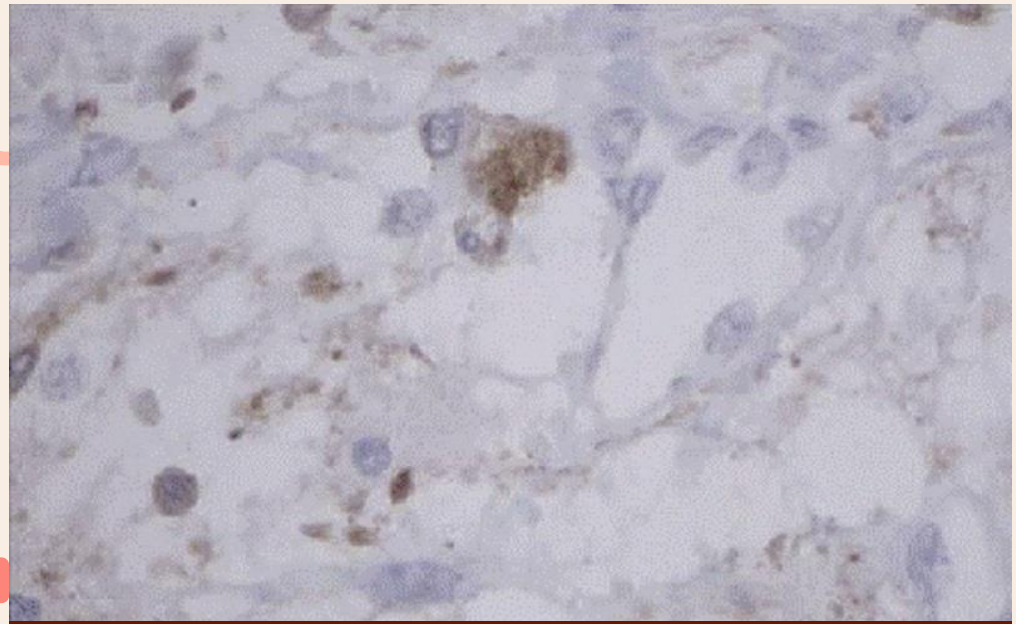
Histologic findings of CP-ganglioneuroma/ganglioneuroblastoma

- Pheochromocytoma: Diffuse **Chromogranin A** and **Synaptophysin** positive
- Positivity of **S-100 for supporting cells** (Schwann cells)
- **Slightly or focal positivity** of **Chromogranin A** and **Synaptophysin** for ganglion cells and neuroblastoma cells
- Staining for **neurofilament proteins** could aid in identification of axon-like processes

- **Immunoreactive VIP predominantly found in neuronal components**
- However, VIP was also positive in pheochromocytoma component

Wang J. et al. *Int J Clin Exp Med* 2017;10(3):4740-4747

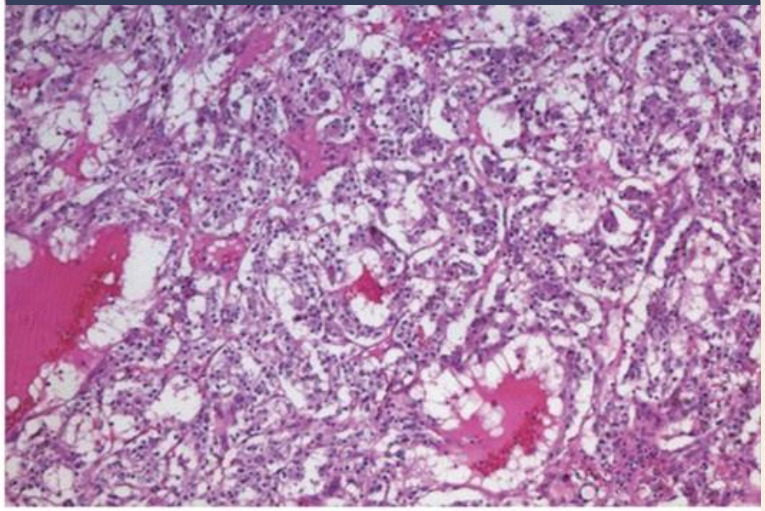




VIP stain in ganglioneuroma component

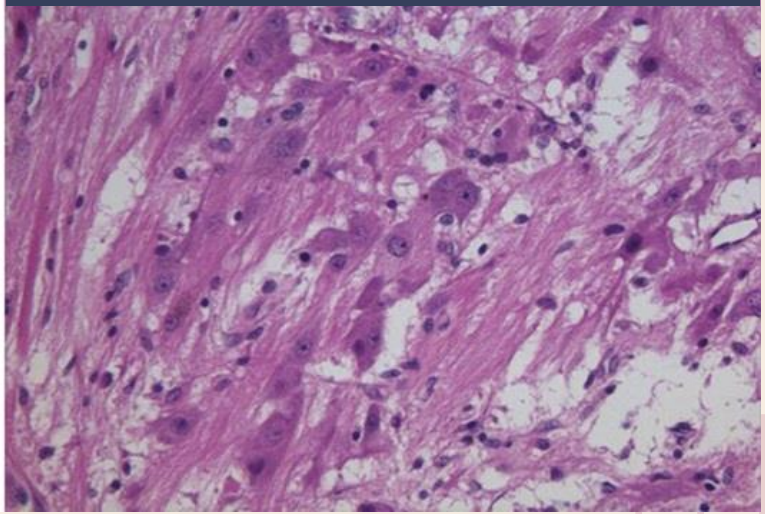
(a)

Nests of pheochromocytoma cells

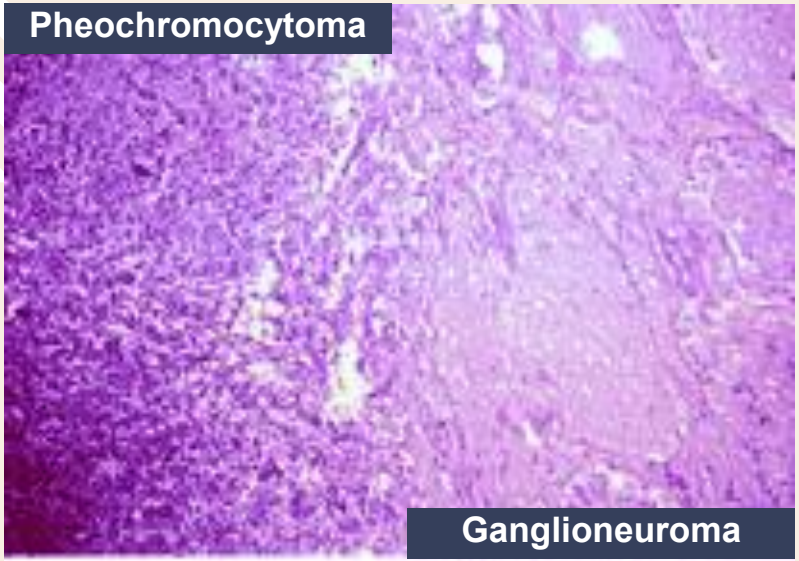


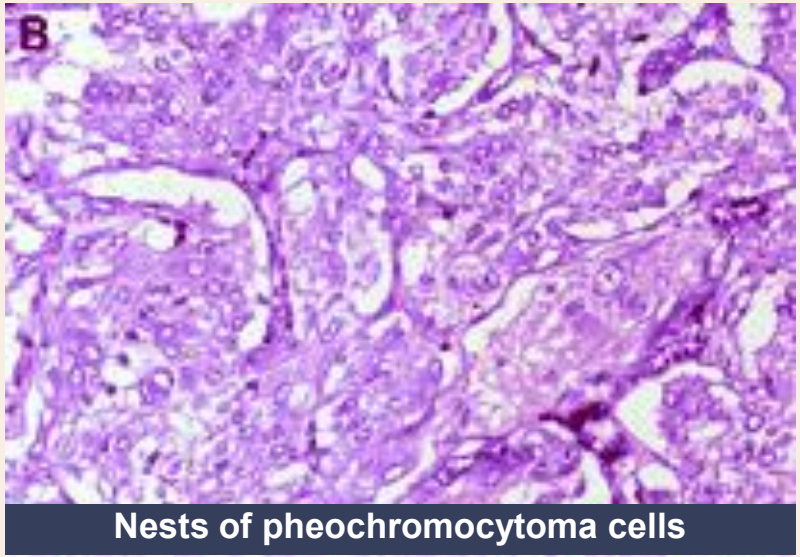
(b)

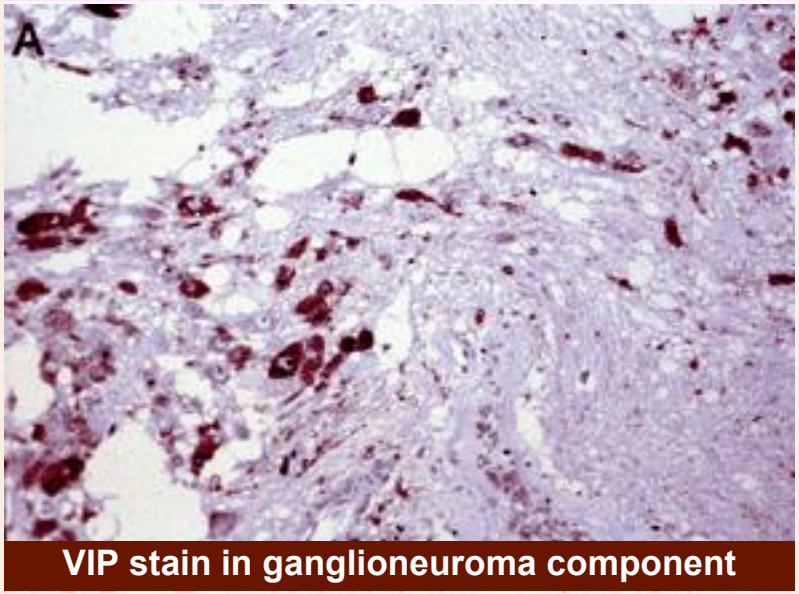
Ganglion cells in Schwannian stroma

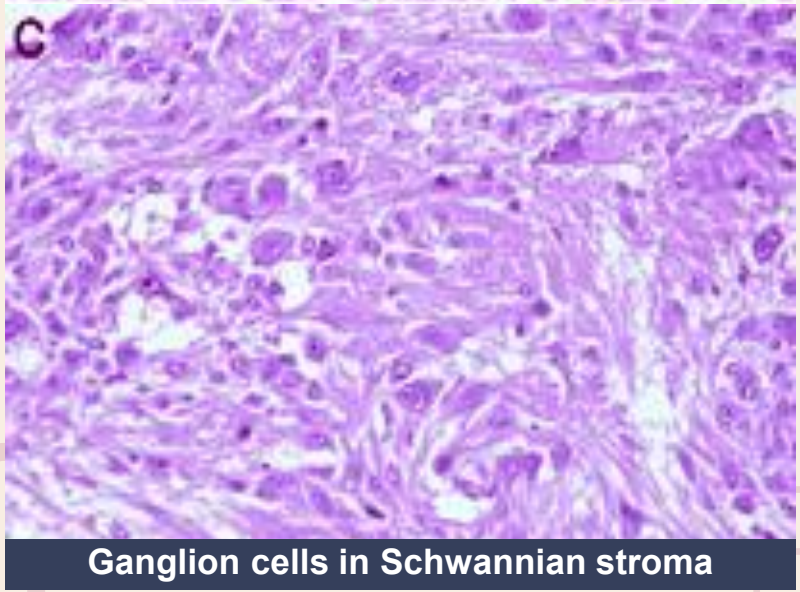


European Journal of Gastroenterology & Hepatology22(5):632-634, May 2010.

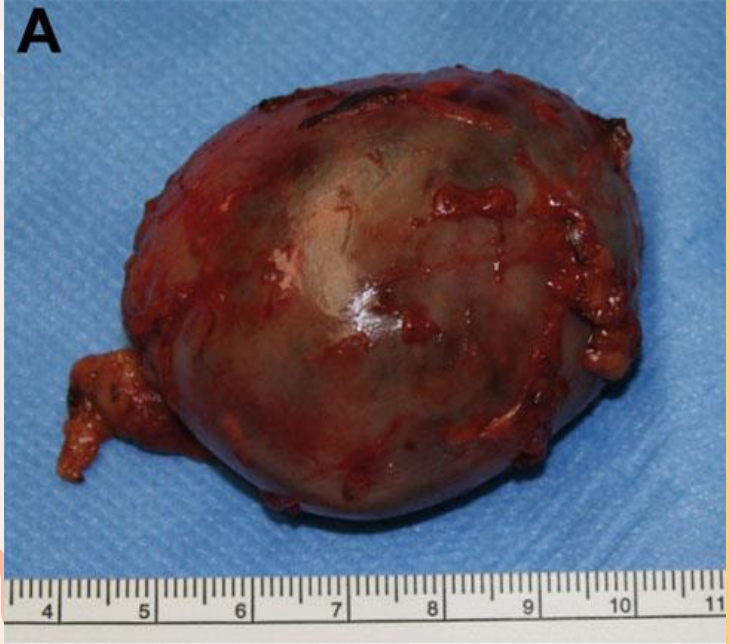


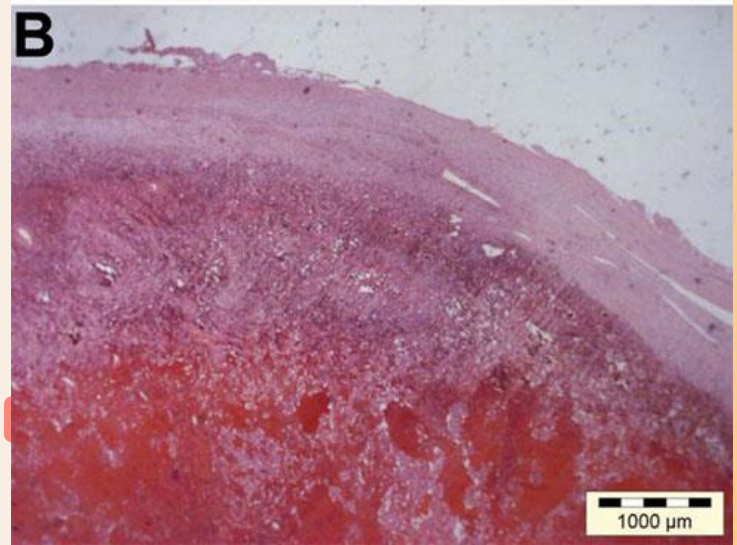


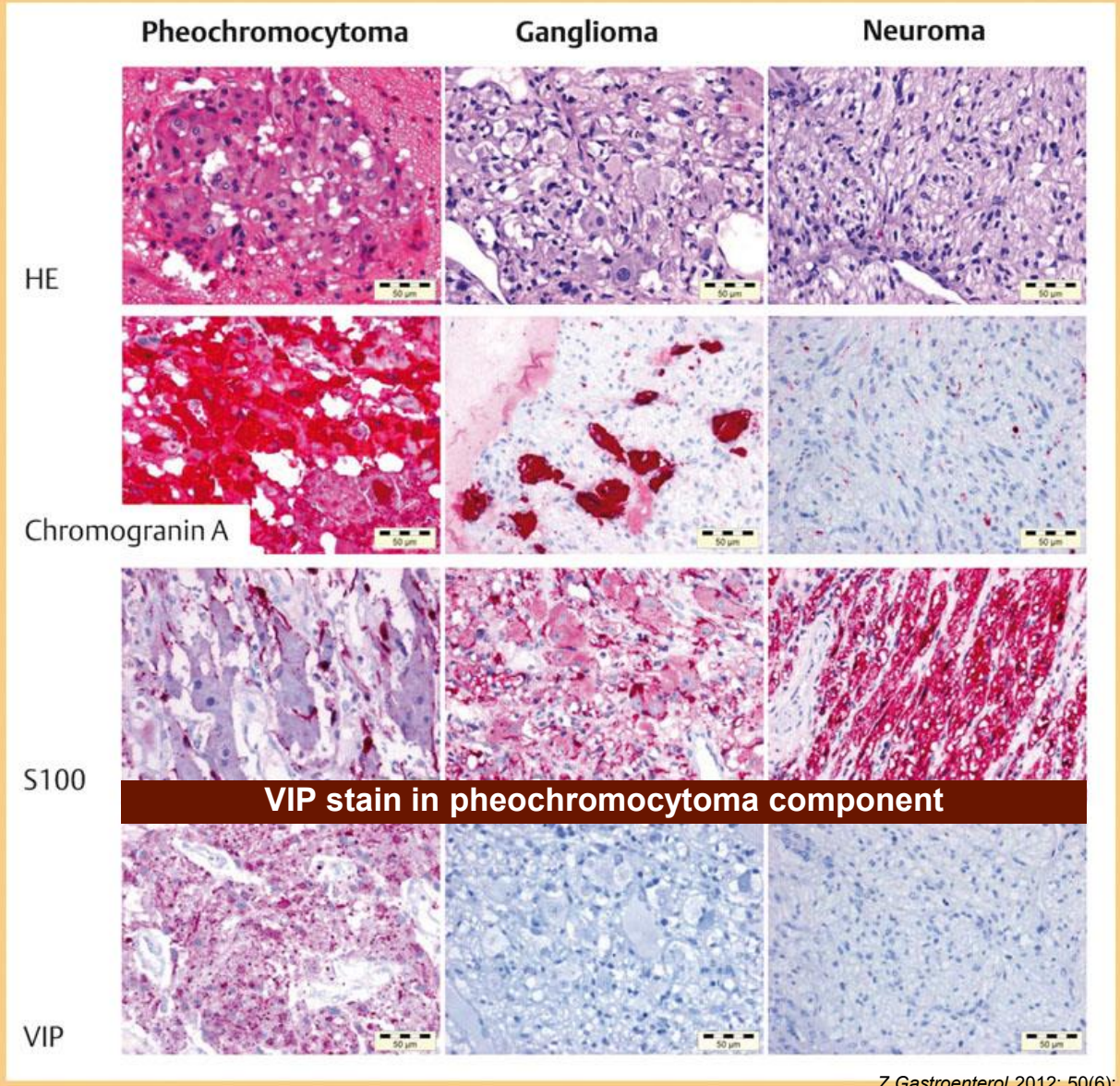




Jpn J Clin Oncol 2005;35(9)559–563







Z Gastroenterol 2012; 50(6): 589-594

Take home message

- Composite pheochromocytoma-ganglioneuroblastoma is extremely rare
- Ganglioneuroblastoma is potentially malignant, therefore, metastasis should be awared
- Vasodilatory effects of VIP may mask the hypertensive effects of catecholamines
- Histologically, immunoreactive VIP was predominantly found in neuronal components of Composite pheochromocytoma
- Composite pheochromocytoma should be considered in VIP-secreting pheochromocytoma

SIENDO
Faculty of Medicine Siriraj Hospital

Thank you