Erdheim-Chester with multiple lesions related to *BRAF* V600E mutation. A simple coincidence?

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Presentation outline

- **Clinical Case**
- **Single Centre Experience Analysis**
- **Review of the Literature**
- **Discussion**

Clinical Case

Mr L.G., 65y

Hypertension, BPH, HBV+

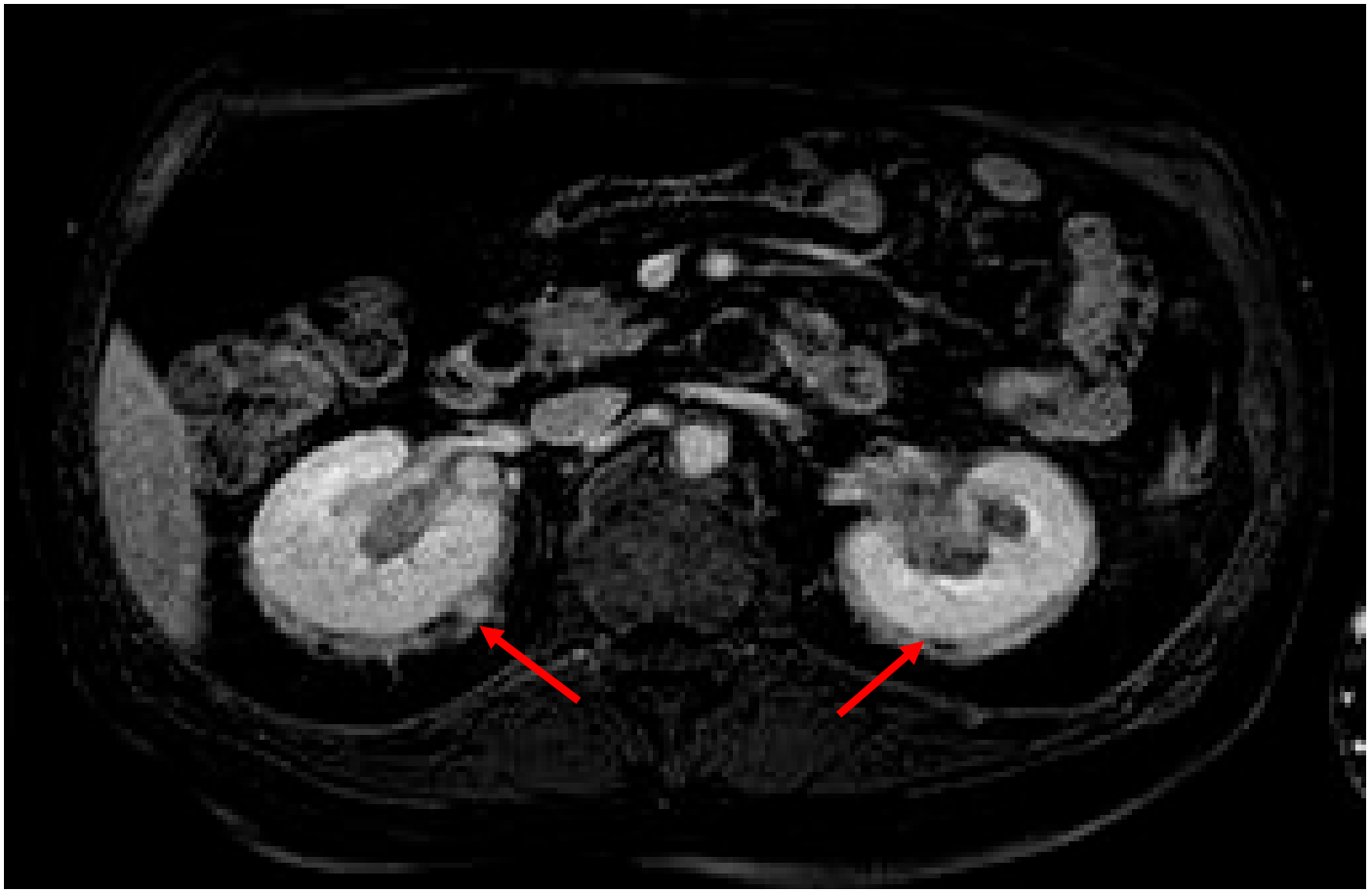
- 2014 → onset of **dysarthria**
- 2015 → onset of abdominal pain with ultrasound evidence of left sided **hydronephrosis**
- July 2016 → abdominal CT-scan: *perirenal and periureteral inhomogeneous hyperdensity causing ureteral and pyelocaliceal dilatation. Hyperdense lesion in the right iliac bone*
- October 2016 → uro CT-scan: *thickening (5 mm) of left renal pelvis, pyelocaliceal junction and proximal portion of left ureter. Right ureter shows parietal thickening causing stenotic obstruction of the lumen and calyceal dilatation. Confirmation of the hyperdense lesion in the right iliac bone*

Clinical Case

- December 2017 → bilateral ureteral stenting
- January 2018 → renal scintigraphy: *reduction of renal transit, consistent with obstructive nephropathy*
- February 2018 → MRI of the brain: *small areas of altered signal consistent with chronic vasculopathy. Periosteal thickening causing partial obstruction of the right maxillary sinus*
- March 2018 → consultation at the Nephrology and Rare Disease Unit of Parma University Hospital (Dr. A. Vaglio): **diagnosis of Erdheim-Chester Disease** (bone, peri-renal and CNS involvement). Hospital admission for diagnostic biopsy

Clinical Case

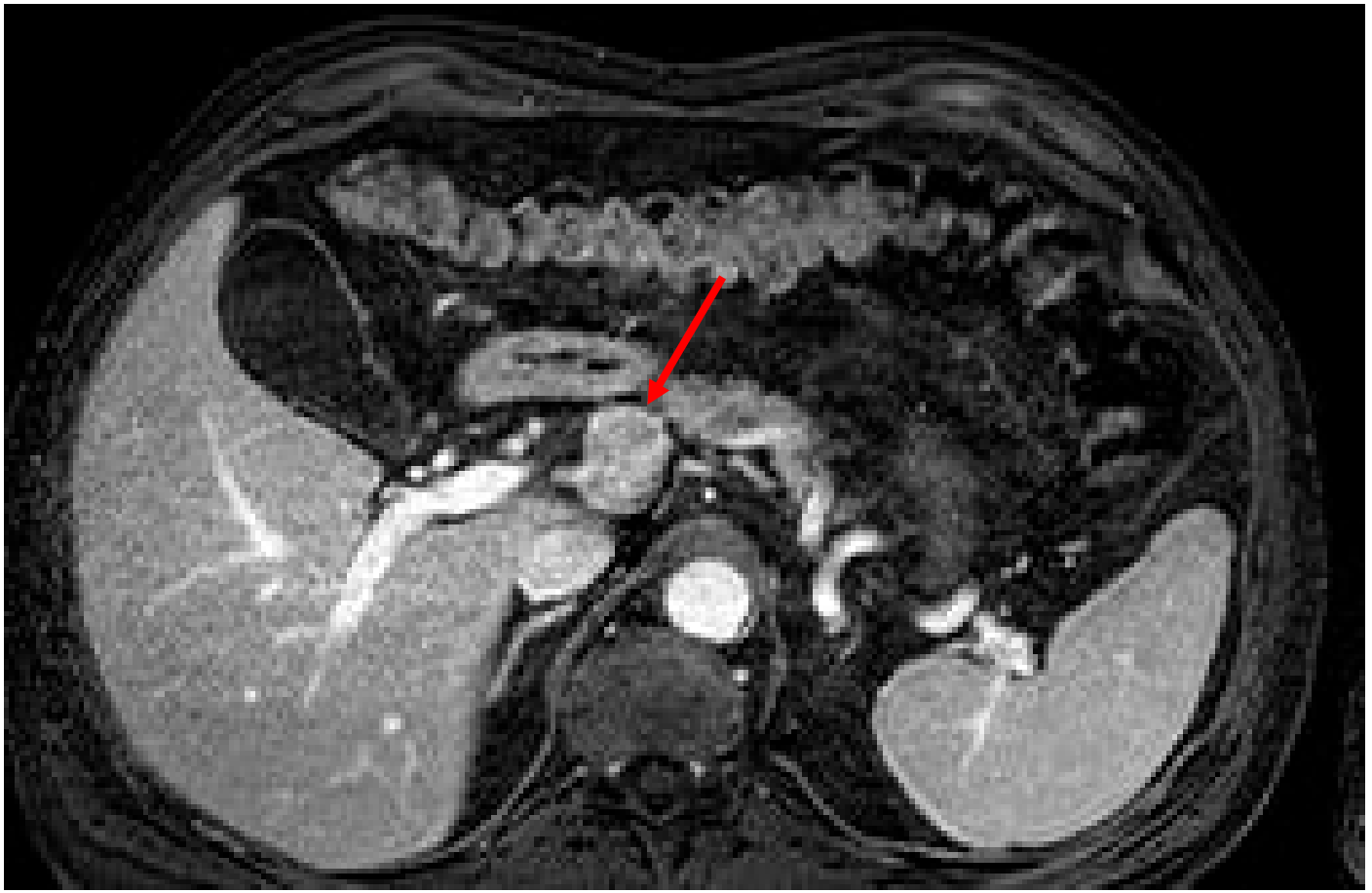
Abdominal MRI (March 2018)



Hypodense perirenal tissue (ECD localisation)

Clinical Case

Abdominal MRI (March 2018)

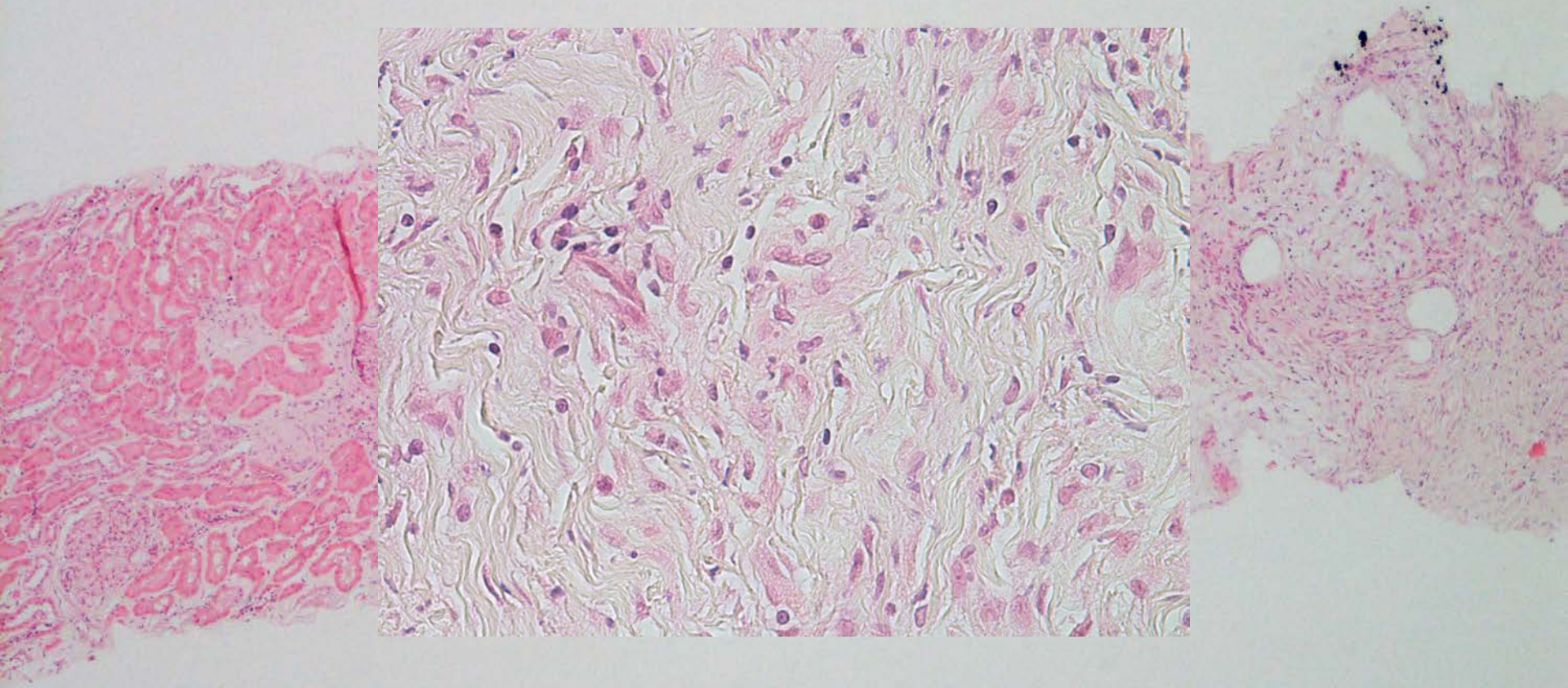


Ovular nodule between pancreas and liver
(29x19mm) with post-contrast enhancement

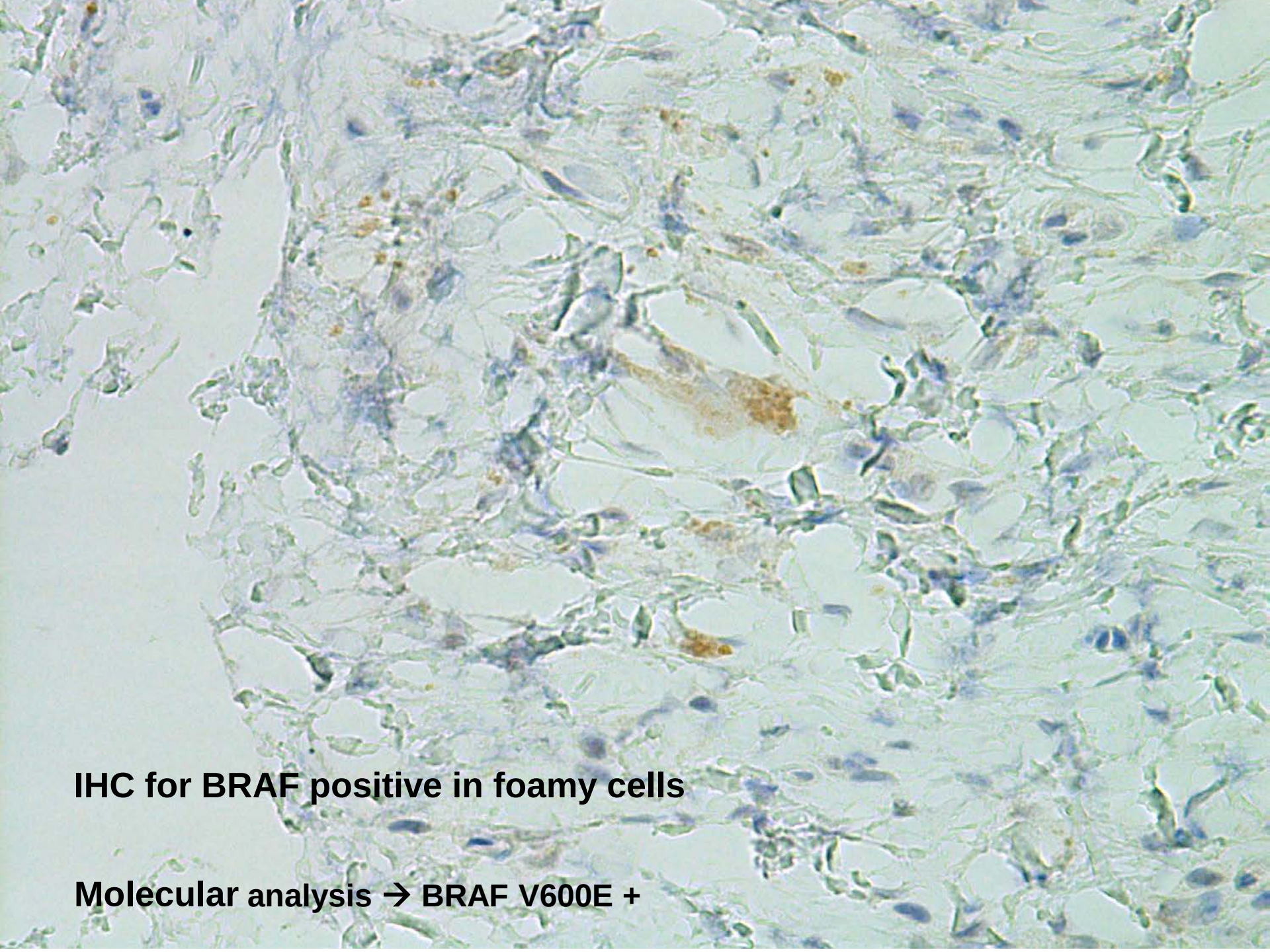
Clinical Case

March- April 2018

- CT-PET → *increased uptake in both femurs (SUVmax 11.8), tibias (5.3) and in a nodular perihepatic lesion*
- *Bone scan* → *ECD-related bone involvement of femurs, tibias and right maxillary sinus*
- Cardiac MRI → *normal shape and function; parietal thickening of IV septum*
- HRCT → *centrilobular solid micronodules (ECD localisation?)*
- MRI of the brain → *infratentorial signal enhancement with thickening of the cerebellar peduncles*
- Perirenal tissue biopsy



Renal biopsy → Erdheim-Chester Disease localisation



IHC for BRAF positive in foamy cells

Molecular analysis → BRAF V600E +

Clinical Case

May 2018 → consultation at the **endocrinology clinic**

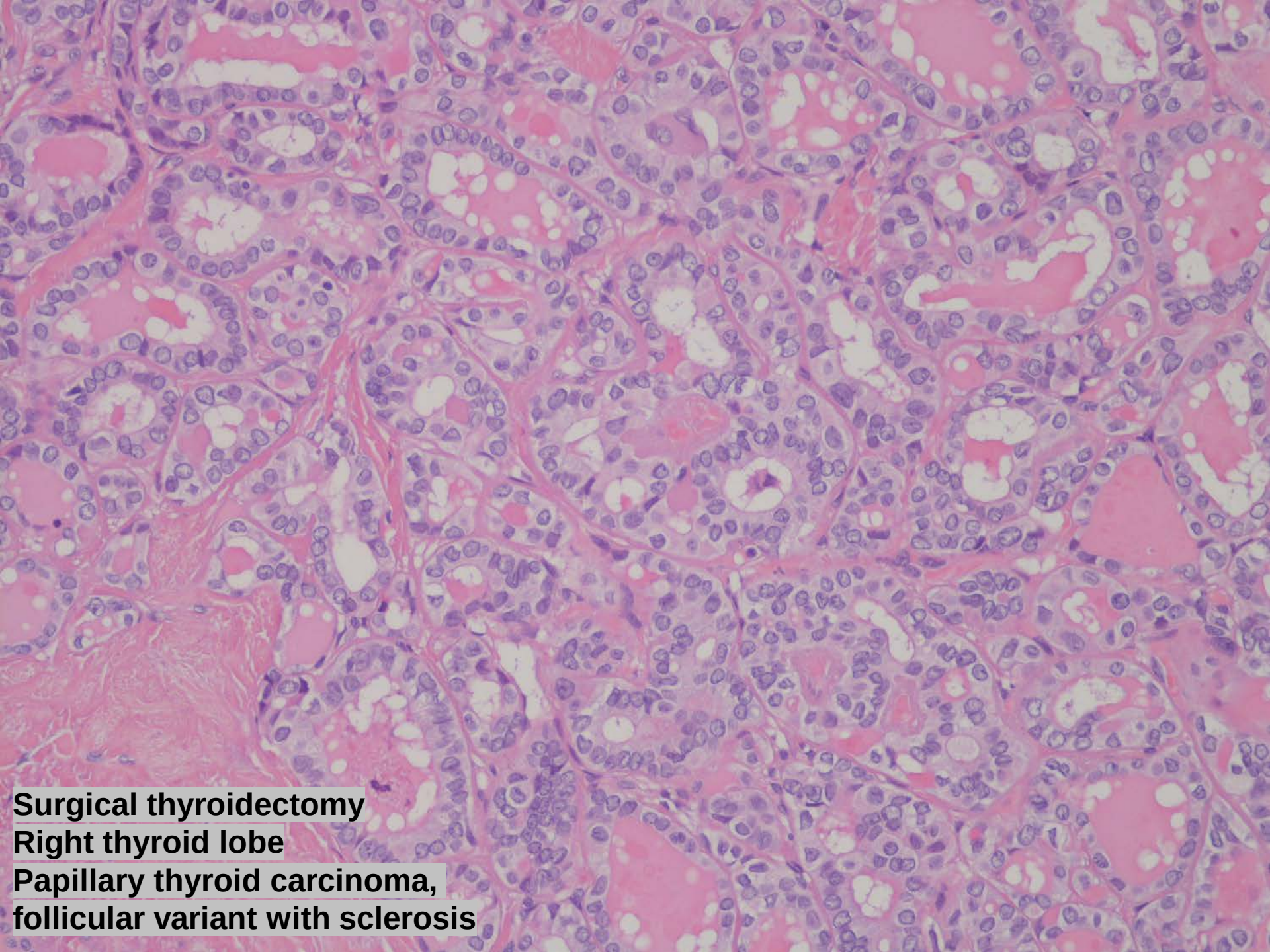
- ✓ Thyroid ultrasound → *right lobe nodular hyperechoic lesion with "taller than wide" shape (4x5x7mm); left lobe nodular hyperechoic lesion (12x8x14mm)*

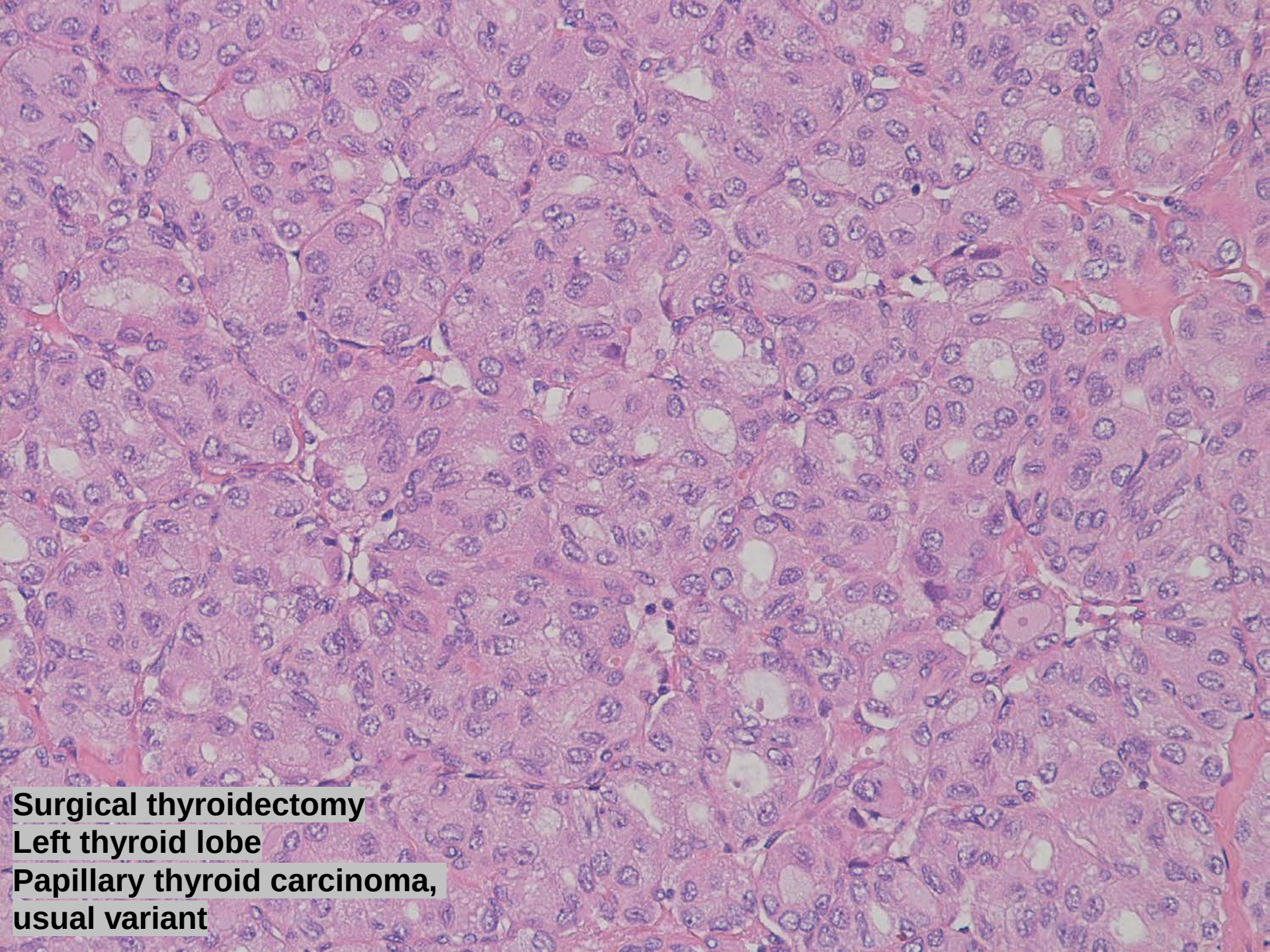
- ✓ Cytology → Thyr 4

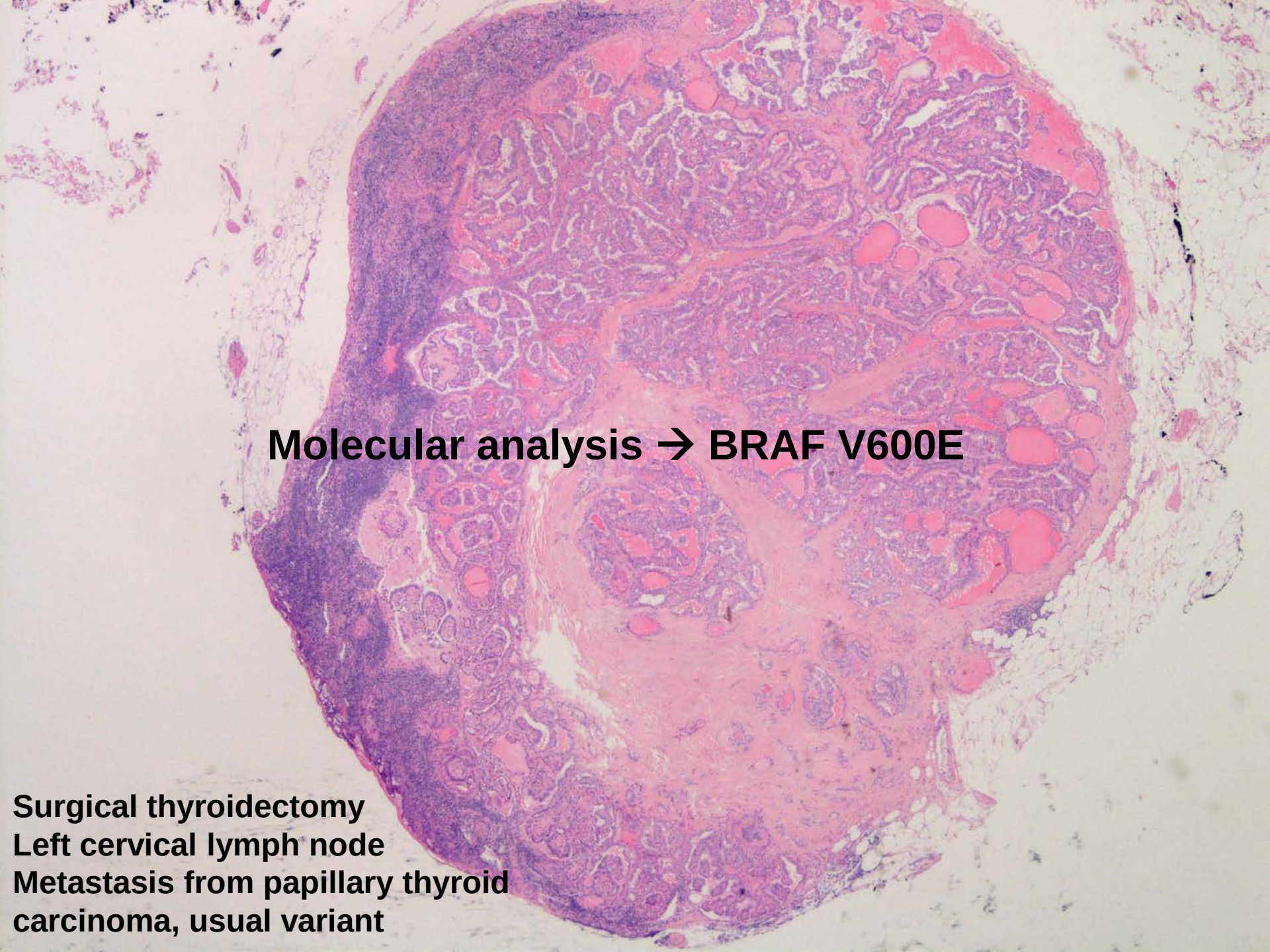
June-July 2018 → hospitalisation for **thyroid and abdominal surgery**

- ✓ Radical thyroidectomy + neck lymph nodes excision

- ✓ Peri-hepatic lymph node excision


Surgical thyroidectomy
Right thyroid lobe
Papillary thyroid carcinoma,
follicular variant with sclerosis

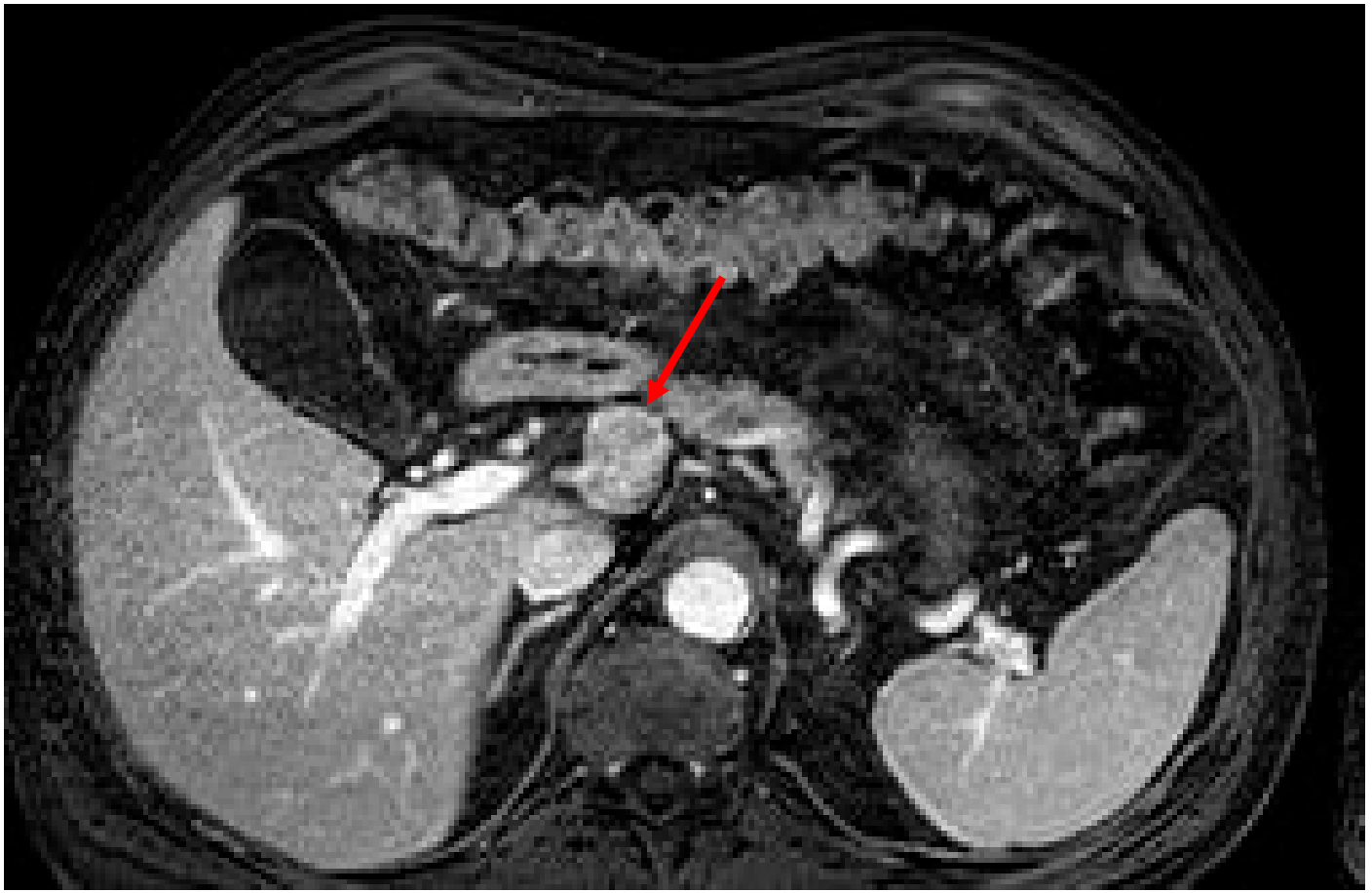

Surgical thyroidectomy
Left thyroid lobe
Papillary thyroid carcinoma,
usual variant



Surgical thyroidectomy
Left cervical lymph node
Metastasis from papillary thyroid carcinoma, usual variant

Clinical Case

Abdominal MRI (March 2018)



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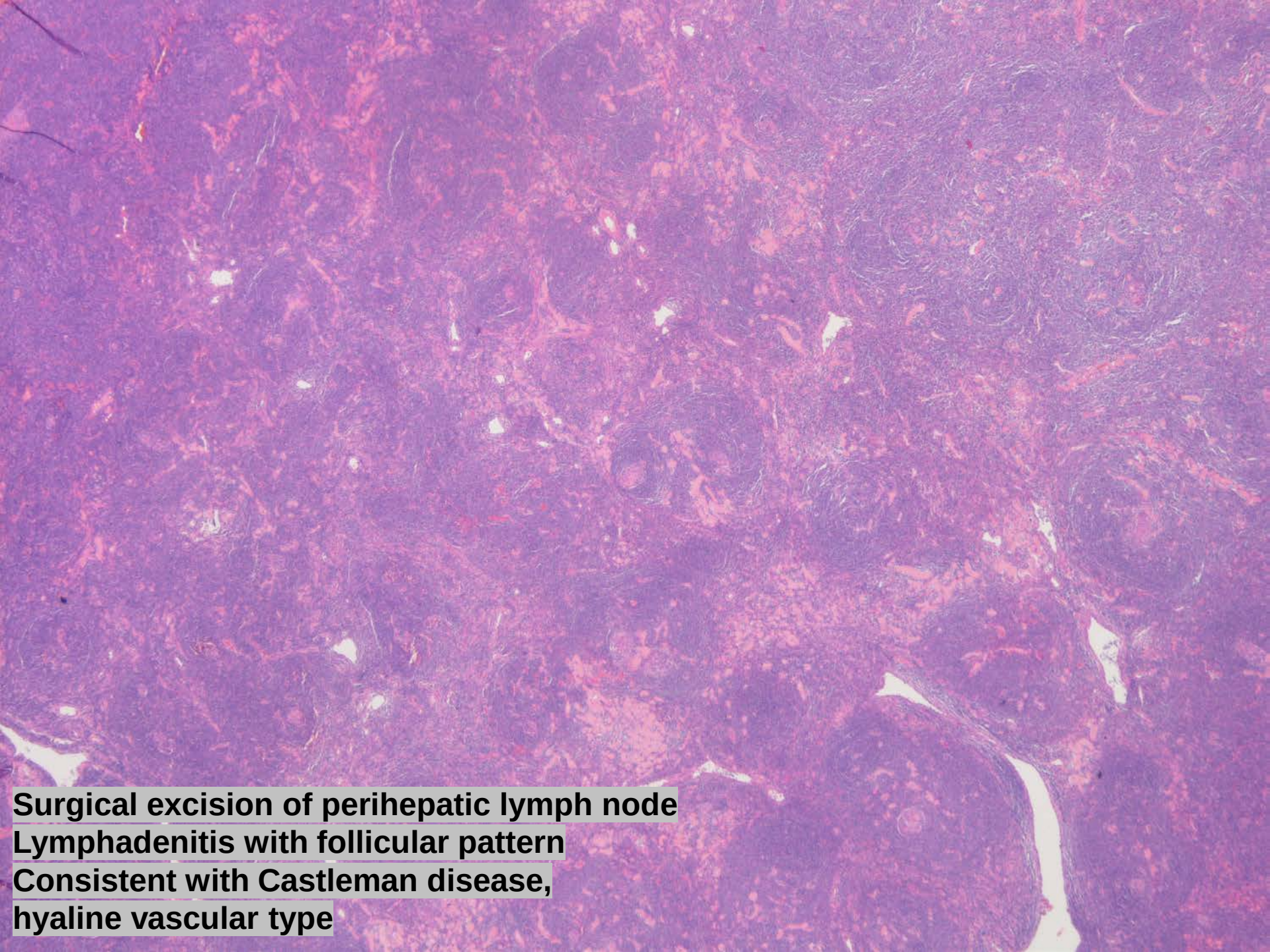
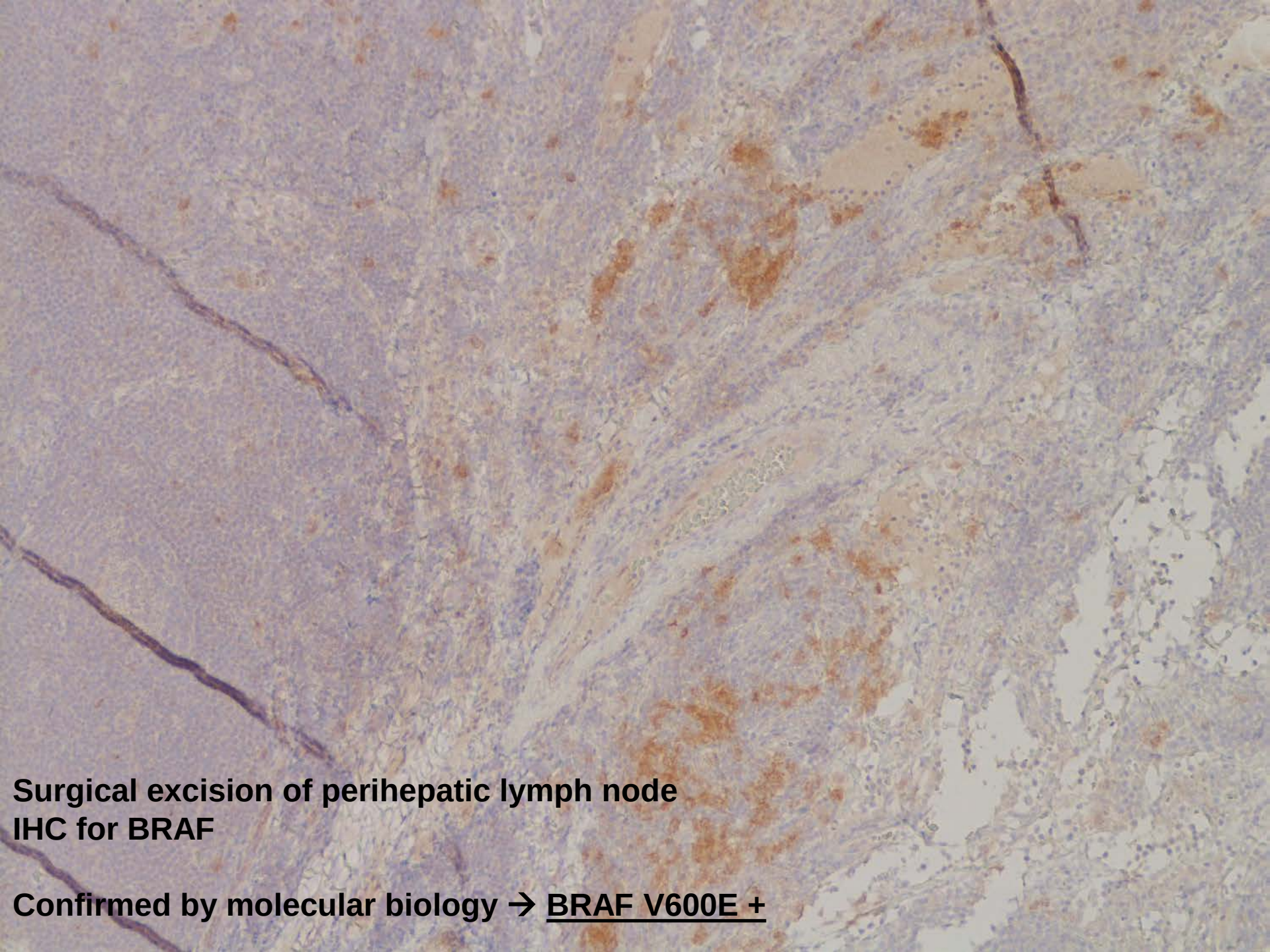


Surgical excision of perihepatic lymph node
Lymphadenitis with follicular pattern
Consistent with Castleman disease,
hyaline vascular type



Surgical excision of perihepatic lymph node
IHC for BRAF

Confirmed by molecular biology → <u>BRAF V600E +</u>

Clinical Case

- September 2018 → 131-I radiotherapy
- December 2018 → Vemurafenib treatment initiation (480mg bid)
- March 2019 → CT-PET disease assessment: *no residual 18-FDG uptake*
- April 2019 → Removal of ureteral stents
- June 2019 → Last follow up: subjective improvement of dysarthria and LUTS

Clinical Case n° 2

A.F., 36 y

- Diagnosed with ECD with bone and renal involvement (advanced CKD) + DI
- BRAF+ on perirenal biopsy
- Screened using thyroid ultrasound, evidence of thyroid nodule
- FNAC Thyr 4
- Radical thyroidectomy + 131-I
- BRAF + thyroid cancer
- Started Vemurafenib (480 mg bid) but progressed to ESRD

Single Centre Experience Analysis

ECD + PTC in our 43 patients case series

- 25 screened using thyroid US
- 2 papillary thyroid cancer
- Single center frequency 8%

Do we have to screen ECD patients for thyroid cancer?

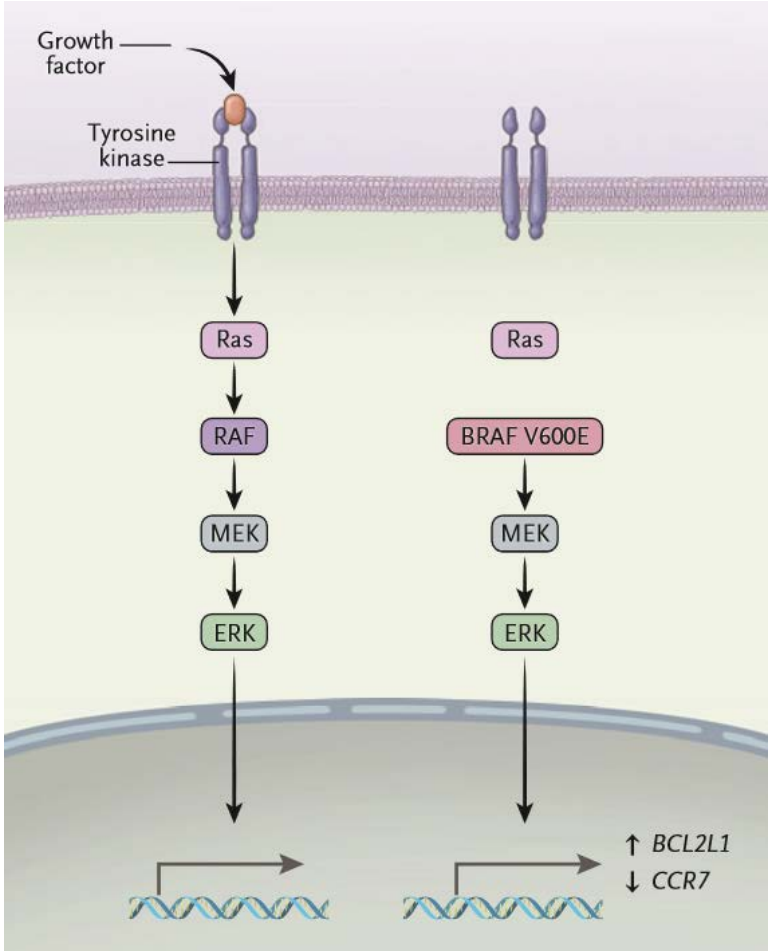
Thyroid Cancer associated with L-group Histiocytosis

Author, year	Sex/Age	BRAF +/- on PTC	LCH/ECD	Non-Thyroid Histiocytosis localisations	BRAF +/- on Histio lesions
Goldstein N, 1991	F/31		LCH	Bone, Pituitary, Lung, Skin, Vagina	
Saiz E, 2000	M/43		LCH		
Foulet-Roge A, 2002	F/42		LCH		
Burnett A, 2008	M/3		LCH	Lung	
Jamaati HR, 2009	M/24		LCH	Lung	
Vergez S, 2010	M/29		LCH	Bone, Pituitary, Lung, Skin	
Chung DH, 2012	F/53		LCH		
Guarino S, 2013	F/22		LCH	Pituitary	
Ceyran AB, 2014	M/37		LCH		
Gordon M S, 2016	F/22	V600E	LCH	Vulva	
Alzahrani R, 2016	F/27		LCH		
Johnson T, 2016	F/38	V600E	LCH+ECD	Bone, Perirenal, Skin	V600E
Wu X, 2017	M/40		LCH	Lung, Liver, Pituitary, Skin	
Jaimanti Bakshi JK, 2018	M/31		LCH		
Al Hamad MA, 2019	F/37	V600K	LCH		V600K

Review of the Literature

Is there, possibly, a link?

Maybe



Allen CE, N Engl J Med 2018

Review of the Literature

NATURE | VOL 417 | 27 JUNE 2002

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14] Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

BRAF mutations were identified in 43 cancer cell lines including 20 of 34 (**59%**) **melanomas**, 7 of 40 (**18%**) **colorectal cancers**, 4 of 38 (**11%**) **gliomas**, 4 of 131 (**3%**) **lung cancers** (all four were adenocarcinomas from a total of 35), 5 of 59 (**9%**) **sarcomas**, 1 of 26 (**4%**) **ovarian carcinomas**, 1 of 45 (**2%**) **breast cancers** and 1 of 7 (**14%**) **liver cancers**

Review of the Literature

BRAF V600 mutation in:

- Melanoma (*Curtin JA, N Engl J Med 2005*)
- Colorectal cancer (*Van Cutsem E, J Clin Oncol 2011*)
- Non–small-cell lung cancer (*Kris MG, JAMA 2014*)
- Papillary thyroid cancer (*Kimura ET, Cancer Res 2003*)
- Diffuse gliomas (*Brennan CW, Cell 2013*)
- Cholangiocarcinoma (*Goeppert B, Mod Pathol 2014*)
- Hairy-cell leukemia (*Tiacci E, N Engl J Med 2011*)
- Multiple myeloma (*Lohr JG, Cancer Cell 2014*)

BRAF V600 mutation is associated with an **aggressive disease phenotype** and **shortened disease-free and overall survival**

Discussion

So is it just a simple coincidence?

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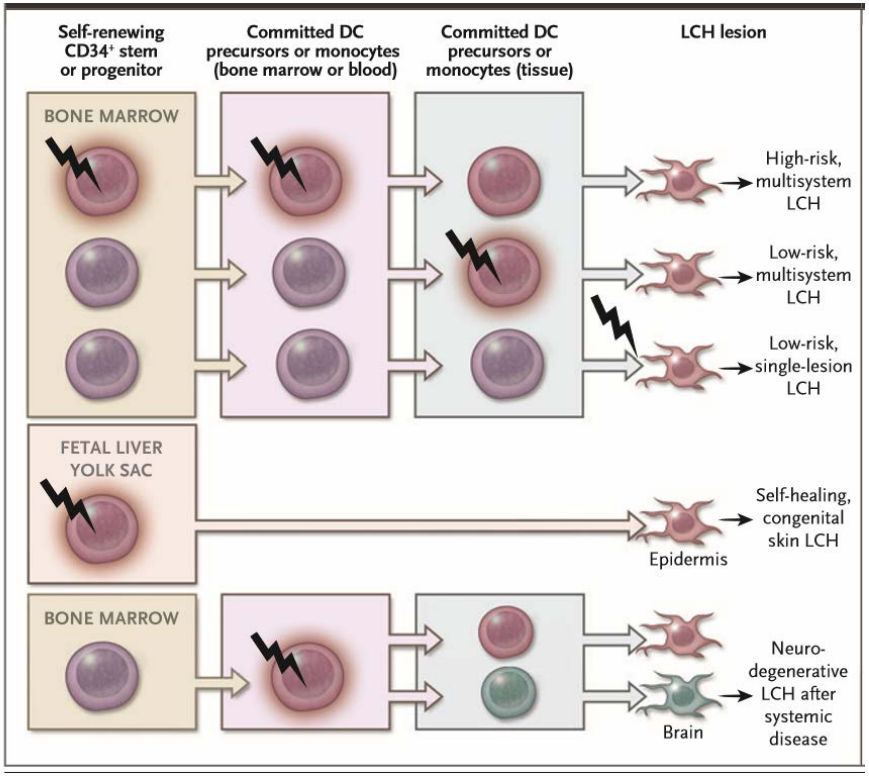

Allen CE, N Engl J Med 2018

Might we have to look upstream?

Discussion

Mosaicism is defined as the occurrence of more than one genetically diverse cell population in an organism

In humans, mosaicism and clonal evolution have been studied most extensively in the hematopoietic system, in the skin and in the central nervous system

- Evidence for an embryonic origin of somatic mutations that lead to cancer comes from the work on childhood acute lymphoblastic leukemia (ALL)

Ford AM, Nature 1993
Wiemels JL, Lancet 1999

- Somatic mutations in cancer genes are found in many congenital skin lesions (which provide a unique opportunity to discover mutations that are necessarily embryonic and can contribute to disease)

Discussion

Mosaic embryonic mutations in *oncogenes* and *tumor suppressor genes* can contribute to tumors in tissues other than the skin or the blood

Fernández LC, Torres M and Real FC, Nature Rev Cancer, 2015

Additional evidence to support an embryonic origin of mutations contributing to cancer in adulthood comes from the study of a small number of individuals in whom the same structural abnormalities present in a bladder tumour are found in mosaicism in leukocytes

Rodriguez-Santiago B, Am J Hum Genet 2010

Skin	Epidermal naevus	*FGFR3*, *PIK3CA*, *HRAS*, *NRAS*, *KRAS* and *FGFR2*
	Melanocytic naevus	*NRAS* and *BRAF*
	Sebaceous naevus or Schimmelpenning syndrome	*HRAS*, *KRAS* and *NRAS*
	Sturge–Weber syndrome, port-wine stains	*GNAQ*
Haematopoietic	Juvenile myelomonocytic leukaemia	*NRAS* and *KRAS*
Intestine	Familial adenomatous polyposis (attenuated)	*APC1*
Bone	Ollier disease	*IDH1* and *IDH2*
Breast	Breast and ovarian cancer	*BRCA1*
Testis	Selfish spermatogonia	*FGFR2*, *FGFR3* and *HRAS*
Multiple tissues	Breast and ovarian cancer	*PPM1D*
	Costello syndrome	*HRAS*
	Phacomatosis pigmentokeratotica	*HRAS*
	Neurofibromatosis type 1	*NF1*
	Neurofibromatosis type 2	*NF2*
	CLOVES	*PIK3CA*
	Klippel–Trelauney syndrome	*PIK3CA*
	Proteus syndrome	*AKT1*
	Cowden syndrome	*PTEN*
	Tuberous sclerosis	*TSC2*
	McCune–Albright syndrome	*GNAS*
	Maffucci syndrome	*IDH1* and *IDH2*
	Li–Fraumeni syndrome	*TP53*

Discussion

Perspectives → BRAF mosaicism study

- ✓ Cutaneous bioptic tissue
- ✓ Blood

A simple coincidence?

Or some new pathogenetic insight?

THANK YOU