Anaplastic Thyroid Carcinoma

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Case presentation

73M w CAD (MI x1, no interventions), T2DM (not on insulin), hx smoking (0.3 ppd x 45y, quit 10y ago), p/w 50lb weight loss, dysphagia, ~4mo enlarging neck mass, found to have AKI and large neck mass on imaging.

TImeline

- 2022-04 intermittent sinus issues began, multiple courses of abx, voice hoarse
- 2022-07-12 PCP visit: noted 36lb weight loss since January. Dysphagia at times. Left face hurts when he lies down. Nontender thryomegaly present on exam. TSH 7.14
- 2022-07-13 US thyroid: left lobe heterogenous

Case presentation

Timeline

2022-08-15 FNA: ATC vs PDTC, but need more tissue for confirmation and ancillary testing

2022-08-19 Core bx:

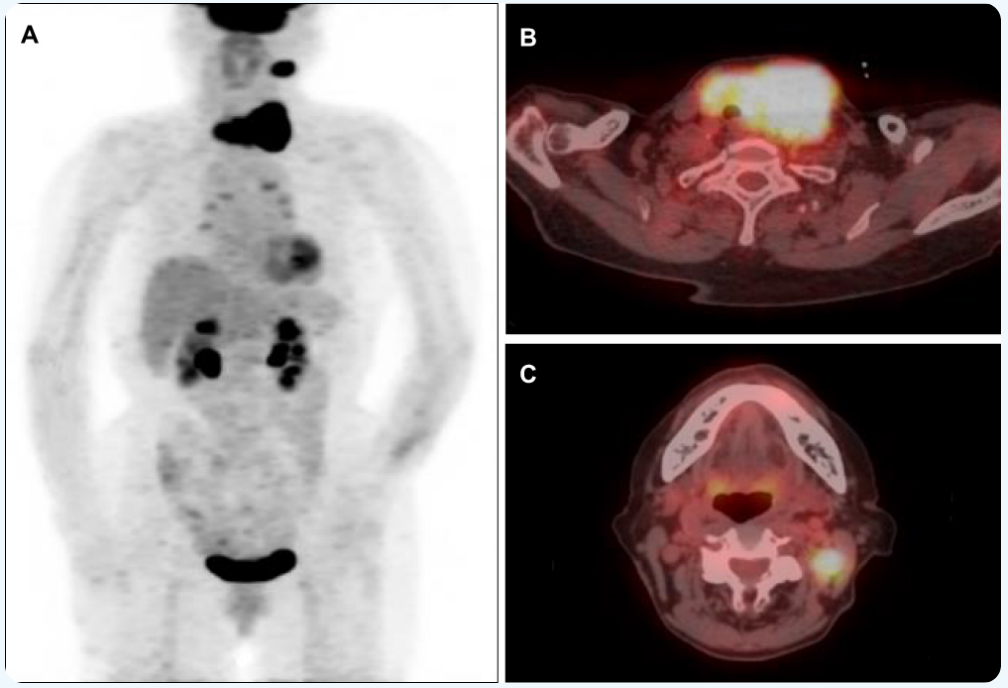
Gross: Sections show an infiltrative malignant neoplasm composed primarily of plump, epithelioid and spindle cells with pleomorphic nuclei, mitotic activity, and background acute and chronic inflammation. In this tumor component, there is no appreciable nesting, squamous, glandular, or other differentiation. There is, however, a focus of a more well-differentiated neoplasm in nests, cords, and small follicles, a few with colloid, which is

Case presentation

CT neck with large left-sided thyroid mass, FDG-PET concordant, with some focal pulmonary avidity.

image source

interactive imaging, representative case



Case presentation

Tumor board

- Surgery: not a surgical candidate (mostly tumor factors)
- RT: planned
- Med onc: let's talk

And then...

- PEG placed
- many discussions w primary, med onc, family
- home w hospice
- died at home 3mo later
  - 11mo from first sx (weight loss)

Questions

What is ATC?

Why is it so gnarly?

What is the prognosis?

What are the key details of workup that change management?

- What kind of imaging should we get?
- Do we need to ask for anything special from pathology?

How was it managed classically?

How is it managed in the modern era?

- What is the role of surgery?
- What is the role of RT?

Epidemiology[1]

thyroid cancers in general:

- 2.5% of all cancers in the US
- 2009 incidence: 37,200
- 2009 death rate: 1,630

ATC:

- 1-2% of all thyroid cancers in the US
- 0.12 per 100,000 person-years (SEER)
- total incidence rising over time (SEER)
  - likely not just better screening or detection

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[1] Smallridge and Copland, "Anaplastic thyroid carcinoma: pathogenesis and emerging therapies," Clin Oncol (R Coll Radiol), Aug. 2010, doi: 10.1016/j.clon.2010.03.013.

Epidemiology

some geographies have higher percent prevalence, up to 10%

differences in percent prevalence appear to be largely driven by general healthcare disparities

percent prevalence has fallen rapidly since the 1960s (25-35%)

- iodine

- fixing earlier-stage thyroid cancers

Epidemiology

median OS: 3-6mo, median 1y survival: 20% (historically)

accounts for up to 50% of deaths due to thyroid cancer

- general thyroid cancer 2009 incidence: 37,200
- general thyroid cancer 2009 death rate: 1,630
- ATC incidence: 2%
- ATC yearly death rate: near 100%
- 37000 * 0.02 = 740

Epidemiology

male:female 1.5:2

typically >60yo

30% have long-standing goiter, then rapid progression

IVa - localized - 10%

IVb - locally advanced - 35%

IVc - metastatic - 55% (lung, bone, liver, brain)

Differentiated thyroid cancer (DTC) component or hx of DTC in 58-90% of cases

Overview (WHO Criteria changed in 2022)

High Grade and Anaplastic Thyroid Carcinomas			
Tumor type	High Grade Follicular Cell-Derived Thyroid Carcinomas (HGFCTC)		Anaplastic Thyroid Carcinoma (ATC)
	Differentiated High Grade Thyroid Carcinoma (DHGTC)	Poorly Differentiated Thyroid Carcinoma (PDTC)	

WHO definition	• Not PDTC
	• ≥1 of the following:
	  • mitotic index ≥ 3 per 10 high power fields
	  • necrosis
		• Not papillary carcinoma
		• Solid/trabecular/insular architecture
		• ≥1 of the following:
		  • mitotic index ≥ 3 per 10 high power fields
		  • necrosis
		  • convoluted nuclei
			• anaplastic (undifferentiated)
			• may have focal areas of healthy differentiation or differentiated carcinoma

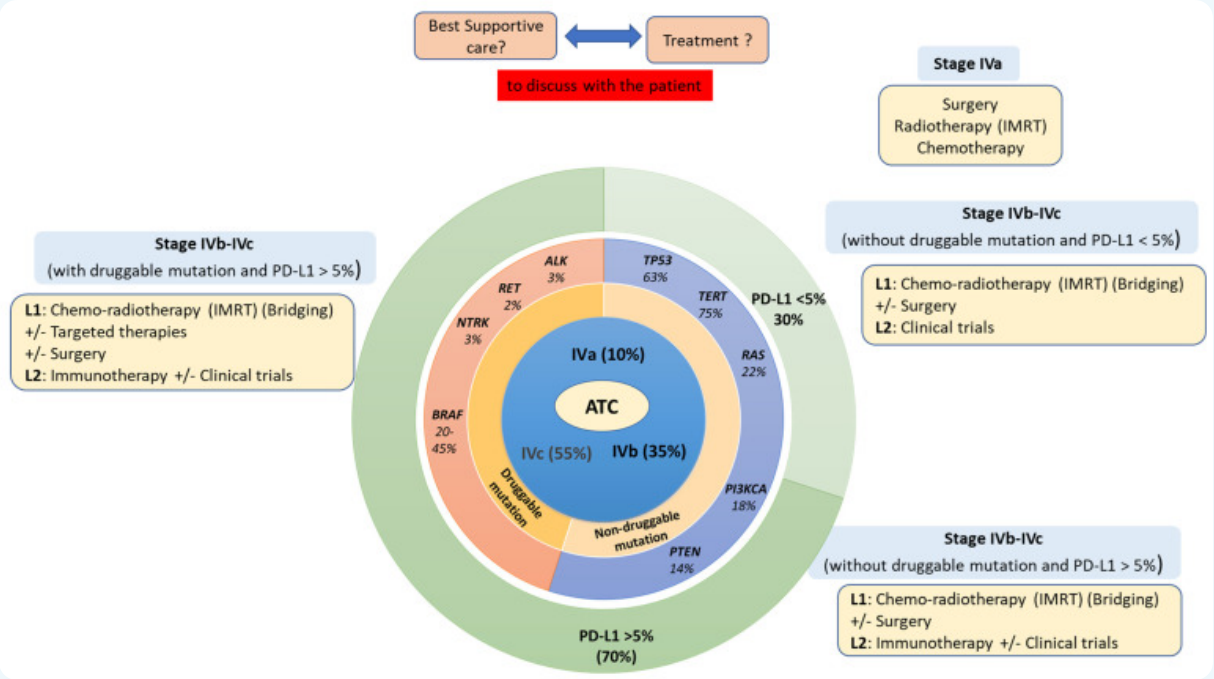
Staging (AJCC 8th Edition)

All ATC is considered stage IV.

	T	N	M
IVA	T1-T3a	N0/NX	M0
IVB	T1-T3a	N1	M0
	T3b	Any N	M0
	T4	Any N	M0
IVC	Any T	Any N	M1

Advanced T stages are defined by extrathyroidal invasion.

Management


Best Supportive care?
Treatment ?
to discuss with the patient
Stage IVa
Surgery
Radiotherapy (IMRT)
Chemotherapy
Stage IVb-IVc
(without druggable mutation and PD-L1 < 5%)
L1: Chemo-radiotherapy (IMRT) (Bridging)
+/- Surgery
L2: Clinical trials
Stage IVb-IVc
(with druggable mutation and PD-L1 > 5%)
L1: Chemo-radiotherapy (IMRT) (Bridging)
+/- Targeted therapies
+/- Surgery
L2: Immunotherapy +/- Clinical trials
Stage IVb-IVc
(without druggable mutation and PD-L1 > 5%)
L1: Chemo-radiotherapy (IMRT) (Bridging)
+/- Surgery
L2: Immunotherapy +/- Clinical trials
PD-L1 <5%
30%
PD-L1 >5%
(70%)
ATC
IVa (10%)
IVb (35%)
IVc (55%)
Druggable mutation
Non-druggable mutation
ALK 3%
RET 2%
NTRK 3%
BRAF 20-45%
TP53 63%
TERT 75%
RAS 22%
PI3KCA 18%
PTEN 14%

Management continued – targets

70% PD-L1 ≥70%

73% TPS ≥5%

10-15% dMMR

20-45% BRAF (dabrafenib-trametinib[1], vemurafenib, cobimetinib)

2-3% ALK (crizotinib, brigatinib, ceritinib)

2-3% NTRK (larotrectinib, entrectinib)

2-3% RET (selpercatinib, praseltinib)

mKI - lenvatinib

Management continued - chemo +/- RT

modest overall benefit, but can be started quickly

typically taxane+platinum or
doxorubicin+taxane/platinum

most prefer regimens with weekly dosing given rapid doubling time

- e.g. carbo AUC2 + paclitaxel 50-100mg/m2
- there's no real data for this, very institution and provider specific

involve RT early for consideration of chemo+RT

Ongoing trials (as of early 2023)

Clinical Trials Gov. Identifier	Treatments/Interventions (Settings)	Phase	Status
NCT03565536	Sorafenib (Neoadjuvant treatment of ATC)	Phase 2	Unknown
NCT03085056	Trametinib + Paclitaxel (Advanced ATC)	Early Phase 1	Recruiting
NCT02688608	Pembrolizumab (Advanced ATC)	Phase 2	Unknown
NCT02244463	MLN0128 (Advanced ATC)	Phase 2	Active, not recruiting
NCT04739566	Dabrafenib + Trametinib (Neoadjuvant Strategy in ATC with *BRAF* mutation)	Phase 2	Recruiting
NCT03122496	Durvalumab + Tremelimumab + Stereotactic Body Radiotherapy (Advanced ATC)	Phase 1	Active, not recruiting
NCT01236547	IMRT + Paclitaxel with or without Pazopanib Hydrochloride (Advanced ATC)	Phase 2	Active, not recruiting
NCT05102292	HLX208 (Advanced ATC with $BRAF^{V600}$ mutation)	Phase 1b/2	Recruiting
NCT02152137	Efatutazone + Paclitaxel (Advanced ATC)	Phase 2	Active, not recruiting
NCT04552769	Abemaciclib (CDK4 + CDK6 inhibitor) (Advanced ATC)	Phase 2	Recruiting
NCT04675710	Pembrolizumab + Dabrafenib + Trametinib (Neoadjuvant *BRAF*-Mutated ATC)	Phase 2	Recruiting
NCT04238624	Cemiplimab + Dabrafenib + Trametinib (Advanced ATC)	Phase 2	Recruiting
NCT04420754	AIC100 Chimeric Antigen Receptor T-cells (Relapsed/Refractory Thyroid Cancer)	Phase 1	Recruiting
NCT03975231	Dabrafenib + Trametinib + IMRT in (Advanced *BRAF* Mutated ATC)	Phase 1	Recruiting
NCT03449108	LN-145/LN-145-S1 (Autologous Centrally Manufactured Tumor Infiltrating Lymphocytes) (Advanced ATC)	Phase 2	Recruiting
NCT04592484	CDK-002 (exoSTING) (Advanced/Metastatic, Recurrent, Injectable ATC)	Phase 1	Recruiting
NCT03181100	Cohort I (*BRAF* mutation): Vemurafenib + Cobimetinib + Atezolizumab. Cohort II (*RAS*, *NF1* or *NF2* mutations): Cobimetinib + Atezolizumab Cohort III (non *BRAF* or *RAS* mutation): Bevacizumab + Atezolizumab Cohort IV: Nab-paclitaxel + Atezolizumab	Phase 2	Recruiting
NCT03246958	Nivolumab + Ipilimumab (Advanced ATC)	Phase 2	Active non-recruiting
NCT04400474	Cabozantinib + Atezolizumab (Advanced ATC)	Phase 2	Recruiting
NCT04579757	Surufatinib + Tislelizumab (Advanced ATC)	Phase 1/2	Recruiting
NCT04759911	Selpercatinib (Neoadjuvant ATC with RET alterations)	Phase 2	Recruiting

Mostly TKI+IO, mostly MD Anderson

Key points

ATC is universally fatal, but early targeted and multidisciplinary intervention can improve outcomes, including extending survival to years in some cases

Call pathology, get BRAF IHC and/or PCR as fast as possible

Even if the mgmt appears to be primarily surgical, involve H&N med onc specialist up front

TKI+IO is an attractive option, but it can be difficult to get IO approved quickly enough to make a difference

- TKI can typically get approved quickly

resection can be beneficial even in the metastatic

Resources

HemOnc.org entry (note - there is no editor for the thyroid sections yet, sparse here)

NCCN Guidelines Thyroid

PathologyOutline ATC

Radiopaedia ATC

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