Cancer of unknown primary site

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Cancer of unknown primary

- per definition a metastatic tumor
- most frequent metastatic sites are: liver, lung, lymph nodes, brain, bone; other metastatic sites rare
- need to exclude common primary tumors

Common modes of metastatic spread

- lymphogenous (regional lymph nodes)
- hematogenous – two theories explaining the pattern of metastatic spread:

- Ewing – based on patterns of circulation (explains frequent occurence of lung metastases)
- Paget – „seed and soil“ hypothesis – favorable microenvironment for certain tumors (e.g. Breast cancer most frequently metastasizes to the bone, uveal melanoma to the liver)

Obligatory investigations to find a primary

- mamography (in women)
- rectal examination
- PSA (in men)
- chest CT (lung cancer; need to distinguish lung metastases from primary lung cancer)
- abdominal CT (liver and pancreatic primary)
- PET/CT leads to diagnosis in 39% of cases
- pelvic examination (in women)
- esophagoscopy, gastroscopy, colonoscopy
- endoscopy of the upper respiratory tract, bronchoscopy
- examination of the testicles (in men)
- skin or eye examination (melanoma)

Only if the results are negative, you may call the diagnosis cancer of unknown primary!

Laboratory investigations

- **Circulating tumor markers of limited value**
- PSA in patients with osteoblastic metastases
- HE4, CA125 in patients with peritoneal carcinomatosis
- betaHCG when germ cell tumors supected
- AFP in hepatocellular carcinoma
- CA19-9 helpful only with extreme concentrations
- Gene profiling/NGS (identification of potential treatment targets)

Classification of tumors based on chemotherapy sensitivity

1. tumors curable by chemotherapy	2. chemotherapy significantly prolongs survival	3. chemotherapy less effective	4. resistant tumors
lymphomas; germinal tumors; pediatric cancer	breast cancer; ovarian cancer	colorectal cancer; gastric cancer; sarcomas	renal carcinoma; melanoma; pancreatic cancer

Even metastatic tumors may be curable!!!

Tumor of unknown primary

- clinical entity
- about 6 % of all metastatic tumors
- primary tumor may be either too small to be detected (1 g of tumor = 10^9 cells), or may regress (melanoma)
- need to obtain precise diagnosis by light microscopy
- immunohistochemistry of poorly differentiated tumors
- refer to specialized centers

Evolution of views on unknown primary cancer

- Separate entity (search for a common effective regimen
- Different tumors responding differently to treatment

Immunohistochemical features of different tumors

tumor	positive staining	negative staining
carcinoma	cytokeratin, EMA	CLA, S-100, vimentin
lymphoma	CLA	
melanoma	S-100, vimentin	
neuroendocrine carcinoma	chromogranin, synaptophysin, NSE	
germ cell tumors	HCG, AFP, EMA	
sarcomas	vimentin	EMA, cytokeratin

EMA epithelial membrane antigen; CLA common leukocyte antigen, NSE neuron specific enolase

Immunohistochemical investigations

	Diagnosis
Step one	
AE1 or AE3 pan-cytokeratin	Carcinoma
Common leucocyte antigen	Lymphoma
S100; HMB-45	Melanoma
S100; vimentin	Sarcoma
Step two	
CK7 or CK20; PSA	Adenocarcinoma
PLAP; OCT4; AFP; human chorionic gonadotropin	Germ-cell tumour
Hepatocyte paraffin 1; canalicular pCEA, CD10, or CD13	Hepatocellular carcinoma
RCC; CD10	Renal cell carcinoma
TTF1; thyroglobulin	Thyroid carcinoma
Chromogranin; synaptophysin; PGP9.5; CD56	Neuroendocrine carcinoma
CK5 or CK6; p63	Squamous cell carcinoma
Step three	
PSA; PAP	Prostate
TTF1	Lung
GCDFP-15; mammaglobulin; ER	Breast
CDX2; CK20	Colon
CDX2 (intestinal epithelium); CK20; CK7	Pancreas or biliary
ER; CA-125; mesothelin; WT1	Ovary

Step one detects broad type of cancer. Step two detects subtype. Step three detects origin of adenocarcinoma. Positive results with any of these stains indicates a tumour is present, but without absolute certainty. PSA=prostate-specific antigen. PLAP=placental alkaline phosphatase. OCT4=octamer-binding transcription factor 4. AFP=α-fetoprotein. pCEA=polyclonal carcinoembryonic antigen. RCC=renal-cell carcinoma antigen. ER=oestrogen receptor. PAP=prostatic acid phosphatase.

	Cytokeratins
Colon	CK7–/CK20+
Stomach	CK7–/CK20+; CK7+/CK20+
Biliary	CK7+/CK20–; CK7+/CK20+
Pancreas	CK7+/CK20–; CK7+/CK20+
Lung	CK7+/CK20–
Ovarian, non-mucinous	CK7+/CK20–
Ovarian, mucinous	CK7–/CK20+; CK7+/CK20+
Breast	CK7+/CK20–
Urothelial	CK7+/CK20+
Endometrium	CK7+/CK20–
Prostate	CK7–/CK20–
Renal	CK7–/CK20–
Liver	CK7–/CK20–

+=positive stain. –=negative stain.

Pavlidis, Pentheroudakis Lancet 2012

Histology of tumors of unknown primary

- adenocarcinoma
- squamous carcinoma
- poorly differentiated carcinoma
- neuroendocrine carcinoma
- germ cell tumors
- melanoma
- lymphoma
- sarcoma
- poorly differentiated neoplasm

Adenocarcinoma of unknown primary

- 60 % of patients with unknown primary
- primary site obvious during life in 20 %
- at autopsy primary detected in 80 %
- lung and pancreas most frequent primary
- median survival 3-4 months
- most effective treatment is combination of taxanes (e.g. paclitaxel), platinum (e.g. carboplatin) and etoposide (median survival 11 months)

Patients with relatively favorable prognosis (20%)

- peritoneal carcinomatosis (papillary/serous histology) in women (occult ovarian cancer of primary peritoneal carcinoma) – paclitaxel-carboplatin
- axillary lymph node metastases in women (occult breast cancer, i.e. stage II-III, curable) – treatment as breast cancer
- increased PSA concentration (in men) – hormonal therapy may be effective
- Squamous cell carcinoma in head and neck region
- Poorly differentiated midline disease in young men (germ cell tumors)
- Metastatic neuroendocrine tumors
- Solitary metastatic tumors
- Adenocarcinoma with colon cancer profile
- Isolated or oligometastatic squamous cell carcinoma in the inguinal region

Poorly differentiated carcinoma

- 30 % of tumors of unknown primary
- need to differentiate lymphoma, germ cell tumors, sarcomas
- may be responsive to chemotherapy (25 % complete response, > 50% partial response)
- long term survival in complete responders (38 % at 17 years)
- preferable treatment combination of paclitaxel, carboplatin ± etoposide

Squamous carcinoma of unknown primary

- cervical or supraclavicular lymph nodes – occult head and neck cancer – radiotherapy or chemoradiotherapy (5-fluorouracil, cisplatin)
- inguinal lymph nodes – primary in the uterine cervix, anus, vulva – radiation, or chemoradiotherapy
- elsewhere – occult lung cancer – regimens for non-small cell lung cancer (e.g. paclitaxel/ carboplatin)

Neuroendocrine carcinoma of unknown primary

- well differentiated tumors (e.g. carcinoid of unknown primary) relatively indolent – therapy octreotide, interferon-α
- small cell carcinoma – chemosensitive tumors – optimal therapy etoposide/cisplatin or paclitaxel/ carboplatin and etoposide
- poorly differentiated neuroendocrine carcinoma – chemotherapy as in small cell carcinoma

Extragonadal germ cell tumors
(rare)

- young men
- mediastinal or retroperitoneal mass
- high HCG or AFP
- pulmonary involvement
- rapid growth
- responding to combination of bleomycin, etoposide and cisplatin

Specific anatomical sites

- liver – difficulty excluding cholangiocarcinoma
- lung – need to distinguish primary and metastatic lesions
- brain – metastases manifest frequently before primary, 2/3 such cases lung cancer
- local disease or skin mass – consider surgical resection, may be the primary (e.g. in the case of sarcoma)

Treatment

- Treatment based on presumed primary
- Directed by the consideration of a potentially sensitive tumor
- In most cases platinum-based (active in NSCLC or ovarian cancer)
- Targetable mutations only in a minority of cases

Conclusions

- in about 6 % of metastatic cancer no primary can be found
- the prognosis is poor, but long term survival (even a cure) may be achieved in selected patients
- a thorough pathological examination is essential
- patients should be referred to medical oncologist with expertise in the field
- paclitaxel/ carboplatin ± etoposide current standard regimen