Coexistence of sarcoidosis and metastatic lesions: A diagnostic and therapeutic dilemma (Review)

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Abstract. Sarcoidosis, a chronic, inflammatory disease that affects various different organs, is characterized by noncaseating epitheloid granulomas. This systemic inflammatory process is associated with an increased risk of cancer. Several cases of sarcoidosis that mimic metastatic tumor progression in radiological findings have been reported so far. However, there are also cases that have presented a coexistence of sarcoidosis and metastasis, which have caused a diagnostic and therapeutic dilemma. Due to inadequate current therapies, a reliable differentiation between benign and malignant lesions is crucial. This review focuses on the residual risk of the coexistence of metastases within radiological suspicious lesions in patients with a history of solid tumors and sarcoidosis, as well as immunological findings, in order to explain the potential associations. Sarcoidosis has the potential to promote metastasis as it includes tumor-promoting and immune-regulating cell subsets. Notably, myeloid derived suppressor cells may serve a pivotal role in metastatic progression in patients with sarcoidosis. In addition, the present review also evaluates the potential novel diagnostic approaches, which may be able to differentiate between metastatic lesions and sarcoidosis. The risk of coexistent metastasis in sarcoidosis lesions must be considered by clinical practitioners, and a multidisciplinary approach may be required to avoid misdiagnosis and the subsequent unnecessary surgery or insufficient treatments.

Contents

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1. Introduction

Sarcoidosis is a chronic, inflammatory, systemic disease affecting primarily the lungs, the mediastinum and the lymphatic system but also salivary glands, heart, nervous system, joints and various other organs (1). Diagnosis depends on the existence of typical clinicoradiological findings in association with noncaseating epitheloid cell granulomas in biopsy and the absence of known, alternative or local causes provoking granulomas (1). Granulomas are nonspecific inflammatory lesions and can occur during mycobacterial, fungal or parasitic infections as well as other diseases like Wegener's granulomatosis (2). Due to the differentiation of granulomas the pathologists play a pivotal role in finding the correct diagnosis (2). In sarcoidosis, granuloma formation is characterized by infiltrating Th1 helper cells and macrophages. The latter show a transformation process into epitheloid cells and can fuse into multinucleate giant cells. Although small amounts of necrosis can be observed, the sarcoid granuloma is referred to the group of nonnecrotizing or noncaseating granulomas (2). Caseating granulomas are typically found in infectious diseases like syphilis or tularemia or infection with tuberculous and nontuberculous mycobacterium (2). In some, especially oncologic patients treated with immunotherapy, noncaseating granulomas can be found although they do not fulfill the criteria for systemic sarcoidosis and are thus referred to as sarcoid-like reactions (3). Due to the toxicity profile of immunotherapies immune-related adverse events can provoke those sarcoid-like reactions which may occur in the organ of tumor origin or in the tumor-draining lymph nodes (3). Sarcoidosis is associated with an increased risk for cancer development in several organs like lung, liver, stomach or for melanoma and lymphoma. Sarcoid-like reactions can be found in 13.8% of patients with Hodgkin-disease, 7.3% with non Hodgkin lymphoma and 4.4% of cases with carcinomas (4,5). Furthermore, simultaneous occurrence of sarcoidosis and cancer is associated with a diminished survival rate (6). Although no increased risk for malignancy in the head and neck has been described so far, there are a few cases that report the simultaneous occurrence of sarcoidosis and malignoma of the head and neck (7-9). Notably, in follow-up computed tomography (CT) scans or those done for the detection of primary tumors or metastatic lesions (e.g., 18-Fluorodeoxyglucose positron emission tomography-(PET)-CT, ^{18}FDG-PET-CT) sarcoidosis can mimic cancer recurrence or metastatic progress (10,11). However, it is possible that metastatic lesions coexist next to lymph nodes with sarcoid-like lesions and it is unclear whether sarcoidosis has an influence on metastasis of malignoma. Therefore, a review of the current literature was performed to analyze the residual risk of metastasis within radiological suspicious lesions in patients with a history of solid tumors and sarcoidosis.

2. Methods

In this review we analyzed reported cases of patients with solid tumors whose staging or follow-up analysis revealed an unclear lymphadenopathy owing to metastasis or sarcoidosis. A systematic literature search was done in Pub Med data base (from inception to April 2017) without any limitation using the terms: Sarcoidosis [title] AND metastasis. All cases with a solid tumor and sarcoidosis were included and the provided information concerning age, gender, tumor region, tumor entity, tumor classification, therapy, as well as information about diagnosis of sarcoidosis were collected. Analyzing the data, the risk of simultaneous occurrence of metastasis and sarcoidosis in concordance to positive radiological and histological findings was elucidated.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent: Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors. For this retrospective study and review of anonymized clinical records an ethical permission was not required.

3. Results

Review of the literature. Review of the literature revealed 115 cases in Pub Med Data Base based on the search criteria mentioned above. Cases without malignancy were excluded and 59 cases with cancer and sarcoidosis were identified and are listed in Table I. The median age at cancer diagnosis was 49.5 +/- 13.4 years and cases of 31 female and 23 male patients were reported. In 5 cases, the sex of the patient was not documented. Systemic sarcoidosis treatment consisted of oral steroids (n=12) or chloroquine (n=1). Local steroids were applied in one case with uveitis. No therapy was initiated in 15 cases and 30 cases did not provide any information about the sarcoidosis therapy approach. However, independent from the treatment strategy the patients' outcome was described to be good with a stable status or complete remission. The most frequent cancer origin was breast (n=12) followed by malignoma of the thyroid gland (n=8). Sarcoidosis occurred in 20 cases after an average of 34.4 months and in 7 cases 10.25 years before diagnosis of malignoma. In most reported cases (n=24) sarcoidosis was revealed simultaneously with diagnosis of malignoma. In 25 cases, surgery was performed to remove the tumor. 24 patients had a combination of surgery and radio-, chemo- or radiochemotherapy. Two cases were only treated by radiochemotherapy and in seven cases, no information about therapeutic aspects concerning the tumor was provided. Occurrence of sarcoidosis after surgery was reported in 3/25 cases and in 17/24 cases after surgery and radio-/chemotherapy. In 17% of the cases, simultaneous detection of sarcoidosis or sarcoid-like lesions and metastasis was reported (n=10). These reports are now described in more detail.

The first case describes a 50-year-old female patient suffering from ductal invasive breast carcinoma with local lymph node metastasis (pT3pN1). Chest X-ray and ^{18}FDG-PET-CT were performed for staging of the tumor and showed a bilateral mediastinal lymphadenopathy and an increased FDG-uptake in supra-diaphragmatic and pelvic lymph nodes. Biopsy of an example lesion obtained sarcoidosis (12). Secondly, an 80-year-old female's CT scan revealed a tumor suspicious mass in the upper lobe of the right lung, multiple smaller nodules and hilar lymphadenopathy. Subsequent biopsy of the mass and a mediastinal lymph node showed just noncaseating granulomas but no malignant cells and led to insufficient treatment. Six months later, symptoms like cough and chest pain were exacerbated and a thoracocentesis revealed adenocarcinoma cells. Further staging examination showed pleural, pericardial and diaphragmatic metastasis. Due to tumor progress, palliative care was initiated (13). The third case describes a 57-year-old female patient who was found to have a choroidal mass in the left eye. Total body gallium 67 scan showed an increased uptake in salivary and lacrimal glands and was misinterpreted as typical for sarcoidosis. Progress of symptoms resulted in enucleation and revealed a choroideal metastasis of a papillary lung carcinoma (14). Sato *et al* (15) report on a patient with concomitant sarcoidosis and lung adenocarcinoma. Thoracoscopic biopsy of altered lymph nodes did not detect metastasis but sarcoidosis. Surgery was performed and a permanent pathological slide showed that several nodes contained both sarcoidosis and lung cancer metastasis (15). Three other reports describe patients suffering from papillary thyroid carcinoma that underwent thyreoidectomy and modified neck dissection. Pathology revealed concurrent existence of sarcoidosis and regional lymph node metastasis (10,16,17). One patient (27-year-old, male) shows a papillary thyroid carcinoma upon a previously diagnosed sarcoidosis. Local lymph nodes contained sarcoidosis mixed with metastasis. A 35-year-old male with a previous history of melanoma developing metastatic involvement and sarcoidosis in regional lymph nodes was described by Chaigne *et al* (18). Khan and Khan (19) described a 52-year-old patient with cough and chest pain. Radiologic examination showed bilateral hilar lymphadenopathy. Furthermore, within a biopsy of an enlarged lymph node, a metastasis of a left kidney hypernephroma was detected (19).

Taken together, these ten patients had a median age of 49 years ranging from 27 to 80 years at the time point of simultaneous detection of metastasis and sarcoidosis. The gender ratio was 0.6:1 (male to female) although no information

Table I. Characteristics of patients from literature review.

	Tumor characteristics				Patient		Sarcoidosis				
Author, year	Tumor region	Tumor entity	TNM classification	Therapy	Age	Sex	Diagnostic tool	Biopsy	Sarcoidosis manifestations	Time between Diagnoses (months)	(Refs.)
Altinkaya *et al*, 2015	Breast	Ductal invasive carcinoma	T1N0M0	OP	70	F	PET	EBUS	LN mediastinal	0	(31)
Conte *et al*, 2015	Breast	Ductal invasive carcinoma	pT3pN1	OP	50	F	PET	OP+Biopsy	LN pelvic, supradiaphragmatic	0	(12)
Zivin *et al*, 2014	Breast	Ductal invasive carcinoma	nk	OP	32	F	PET	Biopsy+EBUS	LN hilar + mediastinal	nk	(32)
El Hammoumi *et al*, 2015	Breast	Lobular carcinoma	T1N2Mx	OP + aRCTx (Tamoxifen)	48	F	CT	Biopsy	LN mediastinal	36	(11)
Kim *et al*, 2014	Breast	Ductal invasive carcinoma	T1N2M0	OP + aRCTx	44	F	PET	Mediastinoscopy	LN paraesophageal, hilar	24	(33)
Akhtari *et al*, 2014	Breast	Ductal invasive carcinoma	T2N0Mx	OP + aCTx + aRT	47	F	PET	FNA	LN supraclav., mediastinal, periportal	0	(34)
Braza and Nelson, 2014	Breast	Ductal invasive carcinoma	T1N0M0	nk	68	F	MRI	Bone biopsy	Lesions lumbosacral spine	nk	(35)
DeFilippis *et al*,2013	Breast	Lobular carcinoma	nk	OP + aRTx	63	F	MRI	Biopsy	LN axillary	0	(36)
Bush *et al*, 2011	Breast	Ductal invasive carcinoma	N0	OP	42	F	PET	Biopsy	LN cervical, abdominal, bone, spleen	0	(37)
Viswanath *et al*, 2009	Breast	Ductal invasive carcinoma	T4aN1M0	OP + aRCTx	50	F	CI	Biopsy	Dermal lesions	24	(38)
Whittington *et al*, 1986	Breast	Carcinoma	N0	nk	nk	F	nk	Mediastinoscopy	LN mediastinal	0	(39)
Whittington *et al*, 1986	Breast	Carcinoma	N0	nk	nk	F	nk	EBUS	LN hilar	0	(39)
El Hammoumi *et al*, 2015	Cervix	Epidermoid Carcinoma	nk	naCTx + OP	47	F	PET	Mediastinoscopy	LN mediastinal	36	(11)
Tamauchi *et al*, 2015	Endometrium	Adenocarcinoma	T1bN0Mx	OP + aCTx	67	F	CT	OP	LN hilar, paraaortic, pelvine	0	(40)
Powell *et al*, 2005	Endometrium	Adenocarcinoma	N0	OP	67	F	CT	FNA	LN mediastinal, liver lesions	48	(41)

Table I. Continued.

	Tumor characteristics				Patient		Sarcoidosis				
Author, year	Tumor region	Tumor entity	TNM classification	Therapy	Age	Sex	Diagnostic tool	Biopsy	Sarcoidosis manifestations	Time between diagnoses (months)	(Refs.)
Takanami *et al*, 2008	Esophageal	Squamous cell carcinoma	N0	OP	72	M	PET	Biopsy	LN mediastinal + hilar	-168	(42)
Takanami *et al*, 2008	Esophageal	Squamous cell carcinoma	pT1b	OP	59	M	PET	Biopsy	LN mediastinal + hilar	0	(42)
Arana *et al*, 2013	Ethmoid sinus	Adenocarcinoma	T3N0M0	OP + aRCTx	42	F	PET	Mediastinoscopy	LN mediastinal + hilar	0	(7)
Kachalia *et al*, 2014	Lung	Adenocarcinoma	TxNxM2	OP	80	F	X-ray	Mediastinoscopy	LN	0	(13)
Kim *et al*, 2011	Lung	Adenocarcinoma	T2N0M0	OP	65	F	PET	Biopsy	LN mediastinal	0	(43)
Mimura *et al*, 2011	Lung	Squamous cell carcinoma	pT1N0M0	OP	69	M	CT	Biopsy	LN mediastinal	-120	(44)
Urushiyama *et al*, 2015	Lung	Squamous cell carcinoma	N0	OP	60	M	CT	Biopsy	LN mediastinal + hilar	-24	(45)
Bouaziz *et al*, 2006	Lung	Squamous cell carcinoma	nk	nk	49	M	MRI	EBUS	LN mediastinal, hepatic nodules	0	(46)
Shields *et al*, 2005	Lung	Papillary carcinoma	M1	OP	57	F	PET	Radiology	Salivary and lacrimal glands, LN hilar	0	(14)
Sato *et al*, 2003	Lung	Adenocarcinoma	N1	nk	nk	nk	nk	Thoracoscopy	LN mediastinal, interlobar	0	(15)
Muramatsu *et al*, 2000	Lung	Squamous cell carcinoma	N0 M0	OP	64	M	CT	Biopsy	LN mediastinal	0	(47)
Abdel-Galiil *et al*, 2008	Maxilla	Squamous cell carcinoma	nk	OP	51	M	PET	Mediastinoscopy	LN mediastinal+ hilar + peribronchial	24	(8)
Yao *et al*, 2005	Oropharynx	Squamous cell carcinoma	T3N2cM0	RCTx	49	M	PET	Mediastinoscopy	LN mediastinal, pretracheal, subcarinal	2	(9)
Yonenaga *et al*, 2006	Ovar	Mucinous Cystadenocarcinoma	nk	OP + aCTx	21	F	PET	nk	Spleen, Liver	36	(48)
Kim *et al*, 2013	Ovar	Papillary cystadenocarcinoma	nk	OP + aCTx	52	F	PET	EBUS	LN paratracheal, supraclavicular, diaphragmal	12	(49)

Table I. Continued.

	Tumor characteristics				Patient		Sarcoidosis				
Author, year	Tumor region	Tumor entity	TNM classification	Therapy	Age	Sex	Diagnostic tool	Biopsy	Sarcoidosis manifestations	Time between diagnoses (months)	(Refs.)
Pollock and Catalano, 1979	Parotid gland	Ductal carcinoma	N2	OP + aRCTx	38	M	CI	Biopsy	LN hilar	-60	(50)
Montini and Tulchinsky, 2012	Rectum	Cancer	nk	nk	45	M	PET	Biopsy skeletal	LN mediastinal,	0	(51)
Abdi *et al*, 1987	Renal	Renal cell carcinoma	N2	OP + aRTx (IFNα)	57	F	CT	EBUS	LN mediastinal	24	(52)
Fukutani *et al*, 1987	Renal	Renal cell carcinoma	NO	OP	75	F	nk	Biopsy	LN pelvic	0	(53)
Khan and Khan, 1974	Renal	Hypernephroma	M1	OP	52	M	X-ray	Biopsy	LN hilar	0	(19)
Gharavi *et al*, 2013	Sacrum	Chordoma	nk	OP	48	M	PET	Biopsy	LN iliacal + femoral	12	(54)
Wilgenhof *et a*l, 2012	Skin	Melanoma	M1c	OP + aCTx (Dacarbazine, Cisplatin)	48	F	PET	EBUS	LN hilar	84	(55)
Vogel *et al*, 2012	Skin	Melanoma	N1	OP + aCTx (αCTLA-4)	49	M	PET	EBUS	LN mediastinal, hilar	168	(56)
Heinzerling *et al*, 2010	Skin	Melanoma	pT4N0M0	OP + aCTx (INFα)	50	M	nk	Biopsy	LN mediastinal	7	(57)
Chiagne *et al*, 2011	Skin	Melanoma	nk	OP	35	M	PET	Biopsy	LN inguinal	0	(18)
Heinzerling *et al*, 2010	Skin	Melanoma	pT3bpN1acM0	OP + aCTx (INFα)	47	M	PET	Biopsy	LN mediastinal+ hilar + peribronchial	nk	(57)
Heinzerling *et al*, 2010	Skin	Melanoma	N1	OP + aCTx (INFα)	47	M	PET	Mediastinoscopy	LN mediastinal+ hilar + peribronchial	2	(57)
Suarez-Garcia *et al*, 2009	Skin	Melanoma	N1	OP + aCTx (INFα)	42	M	CI	Biopsy	Dermal lesions	3	(58)
Massaguer *et al*, 2004	Skin	Melanoma	nk	CTx (IFNα)	nk	F	CT	Mediastinoscopy	LN mediastinal	nk	(59)
Matsubara *et al*, 2015	Stomach	Adenocarcinoma	N0	OP	64	F	nk	Endoscopy	Gastric sarcoidosis	-120	(60)

Table I. Continued.

	Tumor characteristics				Patient		Sarcoidosis				
Author, year	Tumor region	Tumor entity	TNM classification	Therapy	Age	Sex	Diagnostic tool	Biopsy	Sarcoidosis manifestations	Time between diagnoses (months)	(Refs.)
El Hammoumi *et al*, 2015	Stomach	Adenocarcinoma	nk	OP + aCTx	59	F	CT	Mediastinoscopy	LN paratracheal	36	(11)
Tissot *et al*, 1985	Stomach	Adenocarcinoma	nk	nk	63	F	OP	Biopsy	Combined gastric lesions	-336	(61)
Claus *et al*, 2012	Testis	Seminoma	T2N0M1	OP + aCTx (Carboplatin)	34	M	CT	EBUS	LN mediastinal	24	(62)
Claus *et al*, 2012	Testis	Seminoma	T1N0M0	OP + aCTx (Carboplatin)	36	M	CT	Biopsy	LN abdominal	0	(62)
Teo *et al*, 2013	Testis	Seminoma	T1N2M1a	OP + aCTx (Cisplatin, Etoposid)	20	M	CT	EBUS	LN mediastinal	60	(63)
Tjan-Heijnen *et al*, 1998	Testis	Seminoma	N2	OP + aRTx	41	M	CT	Mediastinoscopy	LN mediastinal	24	(64)
Salih *et al*, 2015	Thyroid	Papillary thyroid carcinoma	T2N1Mx	OP	48	F	X-ray	Neck dissection	LN cervical and hilar	0	(10)
Lebo *et al*, 2015	Thyroid	Papillary thyroid carcinoma	T1bN1aMx	OP	41	F	PET	Mediastinoscopy	Cervical + mediastinal	0	(16)
Myint *et al*, 2015	Thyroid	Papillary thyroid carcinoma	nk	OP + I-131	68	F	PET	Bone biopsy	LN hilar + mediast. Bone	nk	(65)
Ergin and Nasr, 2014	Thyroid	Papillary thyroid carcinoma	N0	OP	nk	nk	nk	OP	Cervical	pre	(17)
Ergin and Nasr, 2014	Thyroid	Papillary thyroid carcinoma	N0	OP	nk	nk	nk	FNA	Cervical	post	(17)
Ergin and Nasr, 2014	Thyroid	Papillary thyroid carcinoma	N1	OP	nk	nk	PET	OP	Cervical	0	(17)
Ergin and Nasr, 2014	Thyroid	Papillary thyroid carcinoma	N0	OP	nk	nk	nk	OP	Cervical	0	(17)
Zimmermann-Belsing *et al*, 2000	Thyroid	Papillary adenocarcinoma	N2	OP	27	M	Scintigraphy	Biospy	LN hilar	-36	(66)

nk, not known; OP, operation; aCTx, adjuvant chemotherapy; aRTx, adjuvant radiotherapy; aRCTx, adjuvant combined radiochemotherapy; naCTx, neoadjuvant chemotherapy; INFα, Interferon alpha; PET, positron emission tomography; CT, computed tomography; F, female; M, male; MRI, magnetic resonance imaging; CI, clinical investigation; EBUS, endobronchial ultrasound based biopsy; FNA, fine needle aspiration; LN, lymph node.

concerning the sex was provided in two cases. In 8 cases (80%), the metastases were localized in regional lymph nodes whereas just 2 cases showed distant metastases. Furthermore, the region and entity of the associated tumor differed greatly (breast: n=1, lung: n=3, thyroid: n=4, skin: n=1, kidney: n=1).

4. Discussion

Sarcoidosis and metastasis. Although there are several published cases concerning coexistence of malignoma and sarcoidosis, the causal relationship between these entities is still unclear. On the one hand, it is possible that patients with sarcoidosis develop malignancies and, on the other hand, there are oncologic patients developing sarcoidosis and sarcoid-like reactions, especially after chemotherapy (3). Several cases describe a mimicking of metastatic disease by sarcoidosis but just a few cases actually report a simultaneous occurrence of sarcoidosis and metastases.

Active sarcoidosis is characterized by an enhanced local expression of T helper 1 (Th1) and T helper 17 (Th17) chemokines and cytokines like IFN-γ, TNF-α, IL-17A and IL-22. In various chronic, autoimmune, inflammatory diseases, such as sarcoidosis, the percentage of IL-17A$^+$/IFN-γ$^+$ double-producing Th-cells is increased in peripheral blood and is related to high disease activity. Furthermore, in these pathological conditions, a dysfunctional response of regulatory T-cells (Tregs) has been described that is characterized by an insufficient immunosuppressive function (20). Interestingly, cytotoxic T-lymphocyte antigen 4 (CTLA-4) expression is decreased while PD-1 (programmed death-1) expression is increased in Th17-cells in the mediastinal lymph nodes during sarcoidosis (20). CTLA-4 is present on Th-cells and mediates an inhibitory effect on further T cells responses. Hence, a diminished CTLA-4 level maintains inflammatory reactions. Similarly, PD-1 is expressed on the surface of T-cells upon activation and is involved in limiting inflammatory reactions (21). Its ligand, PD-1L, can be found on tumor cells and provokes upregulation of PD-1 in T cells. Consequently, activation of tumor antigen-specific T-cells in pancreatic adenocarcinoma is inhibited (22). Hence, the bivalent adaptive immune response in patients with sarcoidosis and metastasis promotes both pathological conditions by maintaining sarcoidosis-related inflammation due to the decreased anti-inflammatory CTLA-4 expression while limiting tumor-specific T cell activation, marked by an increased PD-1 expression, that enables tumor escape from the immune system and metastasis. Increased PD-1 expression on T-cells in sarcoidosis lymph nodes could thus be a possible predictor of metastasis on the basis of sarcoidosis. Furthermore, myeloid-derived suppressor cells (MDSC) might play a pivotal role in the pathogenic association between sarcoidosis and metastasis. MDSC pursue immunoregulatory and T-cell suppressive functions (23). Although it has not been described yet, an influence of MDSC on sarcoidosis is assumable because of their important role in other inflammatory diseases (24). Th-17 cells are the main source of IFN-γ production in sarcoidosis and IFN-γ induces MDSC differentiation and promotes their immunosuppressive function (20,25). In cancer models, MDSC accumulation was promoted by several cytokines and growth factors, such as IL-6, IL-1ß and S100A8/A9, resulting in an anti-inflammatory tumor microenvironment (23). MDSC themselves express cytokines and chemokines like IL-6, TNF, IL-1β, IL-23 and S100A9 and have the potential to attract both further myeloid cells and tumor cells (26). Furthermore, in a melanoma and lung carcinoma mouse model, S100A9 expressing MDSC were identified as important players in enabling tumor metastasis (27). Consequently, they are generally recognized as dominant tumor-promoting forces (28). Patients suffering from sarcoidosis have increased serum levels of S100A8/A9 and an enhanced cytoplasmatic S100A8/A9 expression in monocytes and multinuclear giant cells in granulomas (29). Because of the sarcoidosis-related inflammation, marked by the expression of IFN-γ, IL-6, IL-23 and S100A8/A9, we can suspect a similar microenvironment to tumors that are characterized by an increased accumulation and immunosuppressive function of MDSC. Accordingly, we can assume that sarcoidosis has the potential to promote metastasis by inducing tumor-promoting and immune-regulating cell subsets. Further analysis is necessary to verify the influence of MDSC on sarcoidosis as well as the cellular immune response concerning the association between sarcoidosis and metastasis.

Differentiation between benign and malignant lesions. PET-CT scan is a very useful diagnostic tool to identify malignant lesions with a sensitivity between 47 and 100% and a specificity of 86-100% (30). Unfortunately, elevated FDG uptake can also be detected in inflammatory diseases such as sarcoidosis causing a diagnostic dilemma. The case of a 61-year-old carpenter with a history of adenocarcinoma of the paranasal sinus and simultaneous occurrence of multiple cervical metastases and sarcoidosis detected during follow-up investigation impressively demonstrates the risk to overlook metastatic lesions within sarcoidosis (Fig. 1). Especially PET scans for staging or restaging of oncologic diseases supply important information about tumor progression. Decisions on curative or palliative therapy are based on this information, emphasizing the importance to avoid misdiagnosis. Inclusion of an additional tracer would be helpful to differentiate between inflammation and tumor. F18-labeled 3'deoxy-3'fluorothymidine (FLT) is such a promising tracer to minimize diagnostic and subsequent therapeutic mistakes. By measuring DNA synthesis instead of metabolic activity that seems to be more specific to detect tumor diseases, FLT might be a useful candidate to discriminate between tumor and sarcoidosis lesions (7).

An additional helpful tool to discriminate inflammatory bone marrow involvement, like skeletal sarcoidosis, from metastatic disease might be the diffusion whole-body magnetic resonance imaging (b-values 50-900s/mm^2). In contrast to malignant lesions (cut-off value of 774 μm^2/s), sarcoidosis or other inflammatory skeletal reactions show high signal intensity on diffusion-weighted images and a lower apparent diffuse coefficient (ADC) (12).

Bioptical evaluation of radiologically altered lymph nodes is necessary for selection of appropriate oncological treatment strategy. However, examination of each PET-CT positive lesion is not feasible and the chance to detect metastatic lesions next to sarcoidosis is rather rare (Fig. 2). Thus, even if pathological findings were suspicious of sarcoidosis, concomitant metastasis cannot be certainly excluded. Hence, correlation between

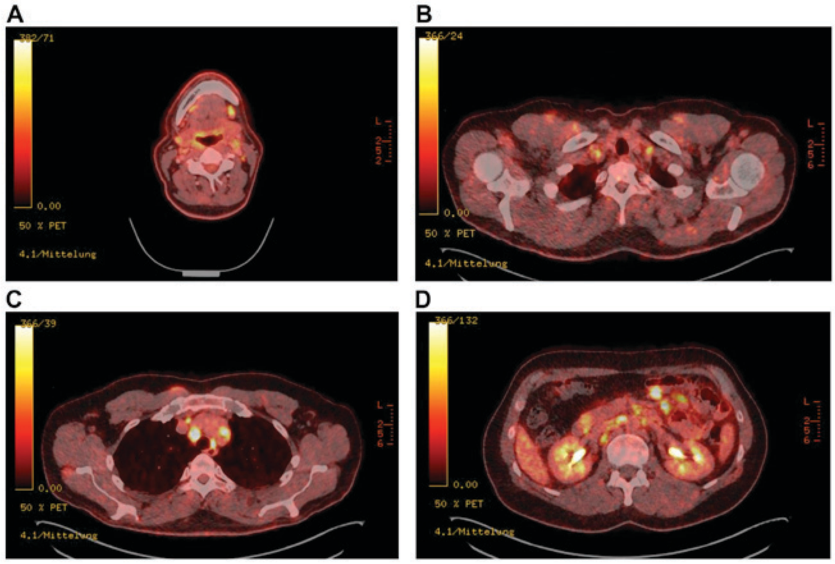

Figure 1. PET-CT showing multiple high uptake lesions: 18-Fluorodeoxyglucose positron emission tomography and computed tomography ([18]FDG-PET-CT) of a patient with a history of paranasal sinus adenocarcinoma shows increased uptake of (A) submandibular, (B) cervical, (C) mediastinal and (D) mesenterial lymph nodes suspicious of multiple metastatic lesions. Bioptical examination revealed cervical metastases of the known adenocarcinoma and mediastinal sarcoid-like lesions without malignancy. Courtesy of Professor W. Heindel, Institute of Clinical Radiology, University Hospital Münster. [18]FDG-PET-CT, 18-fluorodeoxyglucose-positron emission tomography-computed tomography.

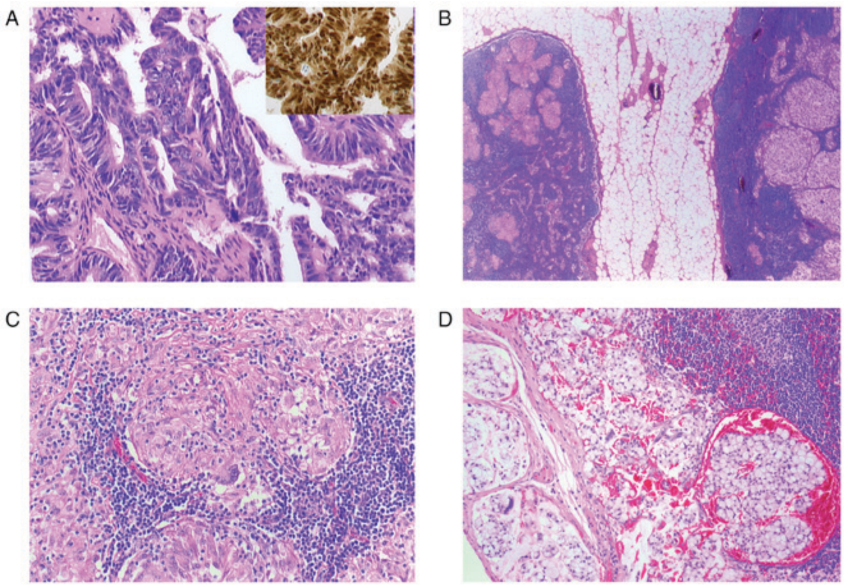

Figure 2. (A-D) Histological findings of a resected paranasal sinus adenocarcinoma and lymph node. (A) Microphotograph shows the adenocarcinoma with atypical tumor cells (H&E; magnification, x400) and CDX2 nuclear positive cells, characteristic for intestinal-type adenocarcinoma (inset, H&E, magnification, x400). (B) Two lymph nodes surrounded by perinodal fat tissue. The right node with noncaseating epitheloid granulomas and the left one with metastatic lesions (H&E, magnification, x5). (C) Lymph node with noncaseating epitheloid granuloma in higher magnification (H&E, magnification, x200). Multinuclear giant cells are identifiable. (D) Metastatic carcinoma infiltration in a lymph node (H&E, magnification, x200). H&E, hematoxylin and eosin; CDX2, caudal type homeobox 2.

the radiological and histological findings with the probability of distant or local metastasis corresponding to the tumor entity is important for the careful assessment of the residual metastasis risk.

5. Conclusion

Correlation between PET-Scan, histological findings and knowledge about typical tumor behavior is necessary to avoid misdiagnosis. Nevertheless, a residual risk of overlooking metastases in systemic inflammatory diseases still remains existent. Therefore, it is important for clinical practice to be aware of the simultaneous occurrence of sarcoidosis and metastatic malignancy. Further cell subset analysis in these pathologies might additionally reveal immunological distinct cell populations as useful markers to distinguish between sarcoidosis, cancer and the coexistence of these two and help in overcoming the current diagnostic dilemma.

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