

Paraneoplastic syndromes in esophageal cancer – a narrative review

Colm Mac Eochagain¹, Karine Ronan¹, Calvin Flynn¹, Zara Togher¹, Jemma Buchalter¹, Maeve A. Lowery²

¹St James' Hospital, Dublin, Ireland; ²Trinity St James Cancer Institute, Trinity College Dublin, Dublin, Ireland

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Correspondence to: Dr. Colm Mac Eochagain. St James' Hospital, Dublin, Ireland. Email: maceochagain@gmail.com.

Objective: This study aims to establish the spectrum of paraneoplastic syndromes reported in association with esophageal cancer with reference to diagnostic criteria, pathogenesis, management, and indicative cases.

Background: Paraneoplastic syndromes are clinical syndromes which arise as a consequence of malignancy, but which cannot be directly attributed to invasion or compression of surrounding organs by the primary tumor or its metastases. Although paraneoplastic syndromes are well described among many solid tumor types, their association with esophageal cancers remains poorly defined. Establishing the spectrum of paraneoplastic sequelae which may accompany a diagnosis of esophageal cancer is important given the rapidly rising incidence of esophageal cancers, the often significant morbidity associated with paraneoplastic syndromes, and the increasing recognition of effective diagnostic and treatment modalities, among a subset of these conditions.

Methods: We conducted a review of paraneoplastic syndromes occurring in association with esophageal cancer. A search was carried out in March 2021 on Scopus, Embase, and Medline (PubMed) databases. The review was prospectively registered with PROSPERO (CRD42020213992).

Conclusions: This review describes the spectrum of paraneoplastic syndromes which have been reported in association with esophageal cancers. We identified 150 articles documenting paraneoplastic syndromes accompanying a diagnosis of esophageal cancer across six broad categories. Individual paraneoplastic syndromes are described with reference to diagnostic criteria, pathogenesis, management, and indicative cases. Case reports are tabulated within their respective subcategories; relevant case series are also discussed within the text. This review may assist clinicians in the timely recognition, diagnosis, and management of these rare conditions.

Keywords: Paraneoplastic; esophageal; esophagus; review; cancer

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Introduction

Esophageal cancer is a common and highly aggressive cancer, responsible for over 430,000 global deaths annually (1). Two predominant histological subtypes are described; globally, the predominant subtype is esophageal squamous cell carcinoma (SCC), however, in many Western

countries, including the USA, the UK, Australia, and much of Western Europe, the incidence of esophageal adenocarcinoma now exceeds that of squamous cell cancers (2). Although age-standardised global incidence is falling, overall incidence is increasing rapidly as a consequence of age-related demographic shifts and increasing global population, with a resultant increase of

52.3% in overall incidence between 1990–2017 (1). Despite significant progress in the treatment of esophageal cancers (3,4), it remains a highly fatal condition, being the sixth most common cause of cancer death globally, with 5-year overall survival rates in the range of 15–25% even among high and middle income countries (5).

Paraneoplastic syndromes are clinical syndromes which arise as a consequence of malignancy, but which cannot be directly attributed to invasion or compression of surrounding organs by the primary tumor or its metastases (6). In general, paraneoplastic syndromes arise as a consequence either of tumor production of physiologically active cytokines, hormones, enzymes, or peptides, which result in end organ dysregulation or dysfunction, or due to immune cross-reactivity between tumor neoantigens and normal tissues.

Although paraneoplastic syndromes are well described among many solid tumor types, including lung (7), lymphoma (8), renal (9), breast (10), prostate (11), gynaecologic (12), and other cancers (6), their association with esophageal cancers remains poorly defined. Establishing the spectrum of paraneoplastic syndromes which may accompany a diagnosis of esophageal cancer is important given the rapidly rising incidence of these cancers (2), the often significant morbidity associated with paraneoplastic syndromes, and the increasing recognition of effective diagnostic and treatment modalities, among a subset of these conditions. All reported paraneoplastic conditions described in association with esophageal cancer are summarized in *Table 1*.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://aoe.amegroups.com/article/view/10.21037/aoe-21-65/rc>).

Methods

We conducted a review of paraneoplastic syndromes occurring in association with esophageal cancer. The review was prospectively registered with PROSPERO (CRD42020213992). A search was carried out in March 2021 on Scopus, Embase, and Medline (PubMed) databases. Articles published between 1970–2021 reporting cases of paraneoplastic syndrome in association with histologically confirmed esophageal cancer, for which a full case description was available, were included. Articles in languages other than English, except where English

language translations were provided, were excluded.

Indicative search strategy included the term paraneoplastic and any of the following: esophagus, oesophagus, esophageal, oesophageal, OGJ, gastroesophageal, esophagogastric, or oesophagogastric. Finally, individual scoping searches were conducted for named paraneoplastic syndromes occurring in association with esophageal cancer. Search results were imported into the Covidence[®] tool for systematic reviews. After removal of duplicates, a total of 634 records were identified, of which 228 were eligible for full text review. Following full-text review, 110 articles were excluded; a further 32 articles were identified through hand-searching of included articles. A total of 150 articles were included in the final narrative synthesis.

Data extraction was conducted by three reviewers (CME, CF, JB). The following minimum dataset was collected: age, gender, anatomical location, histological subtype, stage (grouped), treatment, and survival. Stage data was grouped wherein early stage: T1/2, N0; locally advanced: T3/4 N0 or TxN1+ and metastatic: M1. Where relevant, case series are referred to within the narrative synthesis but typically were not eligible for tabulation due to missing data.

Paraneoplastic syndromes are described with reference to diagnostic criteria, pathogenesis, management, and indicative cases. Given the overlap in the diagnosis, treatment and management common to paraneoplastic neurological syndromes (PNS), the management of these syndromes is discussed collectively. Although constitutional syndromes common to almost all cancer types, such as fever, cachexia, fatigue, anorexia, and depression, could be considered as paraneoplastic phenomena, these were not considered in this review. Reports of syndromes which primarily related to, and which were sufficiently explained by, local tumoral involvement were excluded. Similarly, reports which were felt by consensus to lack causal plausibility were excluded. Causal plausibility was assessed by consensus, taking the following factors into account: availability of a comprehensive case description; original author's conclusion regarding causality; temporal association; response to therapy; potential confounding related to exposure to cancer-directed therapies; potential confounding related to the presence of metastatic disease; potential confounding related to the presence of a synchronous malignancy; and historical documentation of the syndrome as a known paraneoplastic phenomenon in other cancer subtypes.

Table 1 Paraneoplastic syndromes associated with esophageal cancer

Neurological
Limbic encephalitis
RPCS
Neuropathy & neuronopathy
Opsoclonus myoclonus
NMO
Necrotising myelopathy
PRES
Dermatological
Acrokeratosis paraneoplastica
AN
Sign of Leser-Trélat
Subacute lupus erythematosus
PNP
Anti-laminin γ 1-pemphigoid
Sweet's syndrome
Disseminated superficial porokeratosis
Granulomatous dermatitis
Erythema gyratum repens
Lichenoid dermatosis
Eruptive melanotic macules
Rheumatological
HOA
DM
HMGCR antibody-associated myopathy
Polymyalgia rheumatica-like syndrome
Renal
MN
IgA nephropathy/Berger's disease
MCD
MPGN

Table 1 (continued)**Table 1** (continued)

Endocrine
Hypercalcemia of malignancy
SIADH
ACTH secretion
Gastrin secretion
Calcitonin secretion
Haematological
GCSF production
Thrombocytosis
Acquired factor V inhibitor
Henoch-Schönlein purpura
Idiopathic thrombocytopenia purpura
Disseminated intravascular coagulation

RPCS, rapidly progressive cerebellar syndrome; NMO, neuromyelitis optica; PRES, posterior reversible encephalopathy syndrome; AN, acanthosis nigricans; PNP, paraneoplastic pemphigus; HOA, hypertrophic osteoarthropathy; DM, dermatomyositis; HMGCR, β -Hydroxy β -methylglutaryl-CoA reductase; MN, membranous nephropathy; IgA, immunoglobulin A; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; ACTH, adrenocorticotropic hormone; GCSF, granulocyte colony stimulating factor.

Description of cases

PNS (Table 2)

Overview

PNS encompass a wide range of clinical conditions affecting both the central and peripheral nervous systems, and result from autoimmune responses against neuronal tissues bearing antigenic similarities to tumoral neoantigens (32-37). Diagnostic criteria for PNS have been established by the European Paraneoplastic Neurological Syndrome Network (33,34), and emphasise (I) a temporal association with malignancy, (II) the presence of stereotypical clinical

Table 2 PNS

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival	Antibody
Limbic encephalitis									
Gritzman (13)	1983	M	71	Squamous	Distal	Metastatic	Palliative	27 months/dead	-
Shirafuji (14)	2012	F	63	Small cell	Mid	Metastatic	Palliative	10 months/dead	Anti-Hu
Mundiyanapurath (15)	2013	-	69	Adenocarcinoma	-	Early stage	RT	8 months/alive	GABA-B
Mc Cormack (16)	2013	M	72	Squamous	OGJ	Locally advanced	Surgery	-/-	Negative
Menezes (17)	2013	M	-	Adenocarcinoma	-	Locally advanced	Surgery	24 months/dead	Negative
RPCS									
Cox (18)	1989	F	60	Small cell	Mid	Locally advanced	Surgery	15 months/dead	-
Sutton (19)	2001	M	55	Adenocarcinoma	Distal	Locally advanced	Surgery	26 months/dead	Anti-Yo
Xia (20)	2003	M	58	Adenocarcinoma	Distal	Locally advanced	Surgery/RT/Chemo	-/-	Anti-Yo
Debes (21)	2007	M	57	Adenocarcinoma	OGJ	Locally advanced	Surgery	24 months/alive	Anti-Yo
Neuropathy & neuropathy									
Khealani (22)	2004	M	57	Adenocarcinoma	Distal	Metastatic	Palliative	2 months/dead	-
Shimoda (23)	2006	F	63	Small cell	Mid	Locally advanced	RT/Chemo	72 months/alive	Anti-Hu
Zilli (24)	2011	M	65	Adenocarcinoma	Distal	Locally advanced	RT/Chemo	24 months/dead	-
Mostoufzadeh (25)	2012	M	82	Epidermoid	-	Locally advanced	RT	4 months/dead	Anti-GD1a, Anti-GD1b, Anti-GM1
Opsoclonus myoclonus									
Rosor (26)	2014	F	47	Squamous	Mid	Early Stage	Chemo/Surgery	24 months/dead	Negative
Hammani (27)	2019	M	59	Squamous	-	-	Chemo	-	Negative
NMO									
Kon (28)	2017	F	70	Squamous	Mid	Locally advanced	RT/Chemo	12 months/alive	Anti-AQP4
Wiener (29)	2018	M	62	Adenocarcinoma	Distal	Locally advanced	Surgery	24 months/alive	Anti-NMO
Necrotising myelopathy									
Urai (30)	2009	F	65	Squamous	Mid	Metastatic	Palliative	7 months/dead	Negative
PRES									
Nakajima (31)	2013	M	58	Squamous	-	-	Palliative	-	-

PNS, paraneoplastic neurological syndromes; M, male; Distal, distal third of esophagus; F, female; Mid, middle third of esophagus; RT, radiotherapy; OGJ, esophagogastric junction; RPCS, rapidly progressive cerebellar syndrome; Chemo, chemotherapy; NMO, neuromyelitis optica; PRES, posterior reversible encephalopathy syndrome.

manifestations affecting any part of the nervous system, and (III) an immune-mediated pathogenesis, which is supported by the frequent presence of specific neuronal antibodies. Broadly, antibodies involved in PNS may be directed against intracellular targets, resulting in a cytotoxic T-cell mediated response, or against neuronal surface antigens, resulting in an antibody mediated response (38).

A diagnosis of PNS may be made where reasonable differential diagnoses, such as metastatic disease, infection, toxic/metabolic disturbances, and non-paraneoplastic autoimmune conditions, have been excluded (34). Three levels of diagnostic certainty are described, namely: “definite”, “probable” and “possible”. Category assignment is on the basis of the PNS-Care scoring system, which assesses clinical phenotype, the presence or absence of neuronal antibodies, and the presence or absence of a malignancy either consistent with the clinical phenotype, or, if not consistent, where tumoral antibody expression has been demonstrated (34).

Clinical signs of PNS frequently precede the cancer diagnosis, highlighting the importance of investigation for underlying malignancy in the work-up of patients who present with clinical features characteristic of these syndromes (6,39). Since immune mediated attack of neuronal tissues often leads to irreversible cell death and permanent neurological dysfunction, early recognition and treatment is critical (6). Where no malignancy is detected despite comprehensive workup, the close association of particular antibodies with specific tumor types may help to further guide such investigations (36), and comprehensive screening should be repeated every 4–6 months for 2 years in patients meeting criteria for both a high-risk phenotype and high-risk antibody (34). Paraneoplastic neurological conditions which have been described in association with esophageal cancer are summarized in *Table 2*.

Limbic encephalitis

Paraneoplastic limbic encephalitis (PLE) is typically associated with lung, breast, and testicular cancers (40), and is characterised by amnesia, anxiety, depression, insomnia, and seizures of subacute onset (41). The syndrome has been described in association with antibodies to intracellular antigens (anti-Hu, anti-Ma, amphiphysin, Anti-GAD) and neural cell membrane antigens (NDMA, VGKC, GABA, AMPA) (42), although a subset of patients will be seronegative (41).

Diagnostic criteria emphasise a combination of clinical and radiological findings in the diagnosis of PLE (42). MRI

brain typically demonstrates T2-weighted abnormalities in the mesial temporal lobes and mesial cortical structures (frontal cortex, cingulate gyrus, and mammillary bodies) (43), which are not gadolinium enhancing (44). Cerebrospinal fluid (CSF) findings are not pathognomonic but are typically abnormal; abnormalities may include elevated protein, lymphocytic pleocytosis, or the presence of unmatched oligoclonal bands (44). Electroencephalogram (EEG) findings typically demonstrate abnormalities in slow-wave activity, with variable prevalence of epileptiform abnormalities (44).

Among patients with esophageal cancer, significant improvement in neurological symptoms in response to immunosuppressive therapy are described by Menezes *et al.* (17) and Mundiyanapurath *et al.* (15). Furthermore, Mc Cormack *et al.* (16) reported complete resolution of neurological symptoms following successful surgical resection of the primary tumor.

Rapidly progressive cerebellar syndrome (RPCS)

RPCS, previously termed paraneoplastic cerebellar degeneration, is typically associated with gynaecological and breast cancers but has also been reported in association with gastrointestinal and lung malignancies (45,46). Over thirty antibodies have been implicated in the clinical syndrome, of which Anti-Yo is the most common. Anti-Yo antibodies target the Cdr2 antigen of Purkinje cells (47), resulting in CD8⁺ lymphocyte infiltration of the Purkinje layer of the cerebellum, irreversible Purkinje cell death, and proliferation Bergmann astrocytes (48).

Clinical features of classical RPCS develop over the course of short months, manifesting as truncal/limb ataxia, dysarthria, nystagmus, and diplopia, resulting in death or occasionally clinical stabilisation with an often severe degree of disability (48,49). Neurological response to immunosuppressive therapy is often poor. All cases of RPCS described among patients with esophageal cancer describe severe, progressive, and irreversible disability despite often aggressive tumor-directed and immunosuppressive treatment.

Neuropathy & neuronopathy

Paraneoplastic disorders affecting peripheral nerves encompasses a wide spectrum of clinical disorders and manifestations (50). Neuronopathies can also present as purely motor, mixed sensory and motor, and autonomic. Within this group, paraneoplastic sensory neuronopathies are the most frequently encountered, and are frequently

associated with anti-Hu antibodies directed against the dorsal root ganglia (51). Anti-GD1a, Anti-GD1b, Anti-GM1 antibodies have been reported by Mostoufizadeh *et al.* (25) in a case of demyelinating polyneuropathy occurring in association with esophageal epidermoid carcinoma. These disorders may also be seen in the absence of onconeural antibodies (51,52). It is important to highlight that direct effects of malignancy and treatment with cytotoxic agents are frequently independently associated with clinically significant neuropathies.

Opsoclonus-myoclonus (OMS)

Among adults, OMS has been reported in association with small cell lung cancer (53,54), breast (55,56), prostate (57), and ovarian cancers (58,59). OMS is characterised by high-amplitude multidirectional, conjugate saccadic eye movements (35), which are frequently accompanied by limb myoclonus, dysarthria, and truncal ataxia (49,60). OMS may be accompanied by behavioural and cognitive disturbance such as anxiety and mood changes (55,61). Distinct from other PNS, OMS may follow a relapsing-remitting disease course (60). CNS imaging is typically normal. CSF may be normal or demonstrate mild pleocytosis with elevated protein (35,49).

The pathogenesis of OMS remains uncertain but may result from disinhibition of the fastigial nucleus or its afferent projections (61). Onconeural antibodies are typically not detected in OMS (35,49,54,61). In keeping with this, neither of the cases of OMS occurring in association with esophageal cancer reported antibody positivity. Both reported cases of OMS occurring in patients with esophageal cancer describe rapid clinical improvement following administration of IVIG (26,27).

Neuromyelitis optica (NMO)

NMO spectrum disorder (NMOSD; formerly, Devic disease) is an inflammatory demyelinating disorder of the central nervous system, occurring in association with AQP4-IgG (62) (also termed NMO-IgG). NMOSD has been described in association with cancers of the breast, lung, thymus, bladder, and prostate, among others (63-65). AQP4-IgG targets aquaporin-4 (AQP4), the predominant water channel protein of the CNS (66), particularly expressed on the foot processes of CNS astrocytes (29).

NMOSD is a relapsing-remitting condition which preferentially affects the spinal cord and optic nerves (67). Although NMOSD shares clinical characteristics with multiple sclerosis, the condition is now understood to

represent a distinct paraneoplastic phenomenon (63,64). Clinical features vary according to the site of disease activity, but typically include visual disturbance or loss, progressive loss of mobility, seizures, and findings related to brainstem involvement, such as olfactory disturbance, diplopia, and cranial nerve palsies (68).

Two cases of NMOSD are described in association with esophageal cancers (28,29). In both cases, radical treatment of the underlying malignancy was associated with significant neurological improvement.

Necrotising myelopathy

Paraneoplastic necrotising myelopathy (PNM) is a rare condition characterised by acute necrosis of the spinal cord without inflammation. PNM has been reported in association with carcinomas of the lung, breast, thyroid, and other sites (69), as well as haematological malignancies, particularly Hodgkin's lymphoma (70). The syndrome is characterised by subacute massive cord necrosis in the absence of identifiable metastatic deposits or vascular abnormalities (71), resulting in flaccid paraplegia with loss of sphincteric control (71,72). The condition shares clinicopathologic features with NMO syndrome, however the association remains incompletely defined (73) despite occasional overlap in the presence of anti-NMO antibodies (74). In the single reported case of necrotising myelopathy occurring in association with esophageal cancer, anti-NMO antibodies were negative (30).

Posterior reversible encephalopathy syndrome (PRES)

Although not classically considered a paraneoplastic neurological syndrome, hypercalcemia-associated PRES has been reported in association with a PTH-producing esophageal cancer (31) and is an important differential diagnosis which deserves mention. PRES is characterised by headache, new-onset seizures, encephalopathy, and visual disturbances (75) disruption to cerebral vascular autoregulation, particularly affecting the posterior brain due to the relative lack of sympathetic innervation in this region. At least three other cases of malignancy-associated hypercalcemia resulting in PRES have been described in the literature (76-78). Treatment of the underlying metabolic derangement is central to management of this disorder.

Treatment approaches

Perhaps understandably given the relatively recent recognition of the immunological basis of these conditions, the heterogeneity both in presentation and in response

to therapy, as well as their overall rarity, treatment strategies for PNS remain poorly defined and are guided predominantly by case series, case reports, and expert opinion rather than by prospectively randomised, placebo controlled studies (79).

Prompt management of the underlying malignancy removes the stimulus of ongoing autoimmunity, and, where such treatment involves the use of cytotoxic agents, may itself result in immunosuppressive effects which can result in symptomatic improvement or stabilisation of the concomitant neurological syndrome.

Clinical benefit from adjunctive immunosuppressive and immunomodulatory agents, such as corticosteroids (80,81), steroid-sparing agents (e.g., cyclosporine), rituximab (82), intravenous immunoglobulin (83), plasmapheresis (84), and cyclophosphamide (81), has also been described, however, response rates vary considerably, and overall success is low (81). Furthermore, the use of adjunct immunosuppressive agents with chemotherapy may both increase the toxicity of treatment (85), and, theoretically at least, attenuate immune control of the tumor itself (81,86).

Paraneoplastic dermatological syndromes (Table 3)

Overview

Many dermatological conditions which are typically not associated with malignancy may also present as paraneoplastic phenomena. McLean's criteria (116), which emphasise a temporal association of the dermatosis with development and diagnosis of malignancy, as well as the parallel course of the dermatosis as a marker of treatment efficacy, have been proposed to guide in the diagnosis of these conditions. Although treatment paradigms vary according to the specific dermatological features of these syndromes, in most cases, treatment involves management of the underlying malignancy plus standard dermatological management of the nonparaneoplastic variants of these conditions. In general, the paraneoplastic variants are less treatment responsive than their benign counterparts (6). Paraneoplastic dermatological conditions which have been reported in association with esophageal cancer are summarized in *Table 3*.

Acrokeratosis paraneoplastica

Bazex syndrome (acrokeratosis paraneoplastica) is characterised by a psoriasiform eruption of acral distribution, most commonly affecting the nose, ears, fingers and toes (88,91). It is frequently associated

with onychodystrophy. Skin lesions are generally well demarcated, and may be violaceous or erythematous. Histological features are nonspecific, most frequently including hyperkeratosis, parakeratosis, acanthosis, focal spongiosis and mixed dermal cell infiltrates. The diagnosis requires correlation of these nonspecific histological features with the clinical context (91,93).

Bazex syndrome is universally associated with malignancy, most commonly with SCCs of the upper aerodigestive tract (88,93). In the majority of cases, skin lesions precede the diagnosis of malignancy. Bazex syndrome accompanying esophageal carcinoma is most frequently described in association with locally advanced or metastatic disease (88-93), and is associated with a poor prognosis (88-90,92,94).

In general, development of skin lesions follows a linear course which mirrors the underlying malignancy, with a flare of the dermatosis typically signalling disease recurrence or metastasis (88), thus correlating with the evolution of the malignancy as a cutaneous marker of disease activity (89,93). Similarly, improvement in skin lesions is often seen with treatment or control of the underlying malignancy (88,94).

Limited responses to topical treatments have been observed (94), with some published reports suggesting response to topical steroids and etretinate (88,117-119). In a typical case, described by Medenica *et al.* (93), surgical resection of an esophageal SCC resulted in a rapid improvement of skin lesions, with subsequent recurrence signalling metastatic relapse.

Acanthosis nigricans (AN)

AN is characterised by hyperpigmented plaques occurring in intertriginous body sites, commonly the axillae and neck (95). Non-malignant AN is associated with a variety of systemic abnormalities; principally metabolic disorders (120). In approximately 20% of cases, AN presents as a paraneoplastic syndrome (121), typically in association with abdominal malignancies (122). Such cases often present with abrupt onset, an atypical distribution (96,97), and without associated features of insulin resistance or obesity (95).

Histopathological findings are of hyperkeratosis and papillomatosis (123). There is some evidence that paraneoplastic AN occurs as a result of the stimulation of keratinocyte epidermal growth factor receptors by tumoral TNF- α secretion (124). However, Matono *et al.* (95) reported immunohistochemical analysis of a resected esophageal SCC and did not detect the presence of TNF- α or EGF, despite post-operative resolution of the AN lesions.

Skin findings typically manifest concurrently with

Table 3 Paraneoplastic dermatological syndromes

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival
Acrokeratosis paraneoplastica								
Grimwood (87)	1987	F	67	Squamous	Mid	Early stage	Surgery	–/–
Douglas (88)	1991	M	82	Adenocarcinoma	Distal	Metastatic	RT	7 months/dead
Viteri (89)	2005	M	51	Squamous	–	Metastatic	–	–/dead
Cabanillas (90)	2006	M	64	Squamous	Proximal	Metastatic	–	<1 months/dead
Poligone (91)	2007	M	62	Squamous	Distal	Locally advanced	RT/Chemo	–/–
Louvel (92)	2008	M	55	Squamous	Mid	Metastatic	Chemo	30 months/dead
Medenica (93)	2008	M	50	Squamous	Distal	Early stage	Surgery	–/dead
Rodrigues (94)	2013	F	73	Squamous	Distal	Metastatic	Palliative	1 months/dead
AN								
Matono (95)	2008	F	62	Squamous	Distal	Locally advanced	Surgery	12 months/alive
Arnjad (96)	2010	M	64	Adenocarcinoma	Distal	Early stage	Surgery	–/–
Varghese (97)	2011	M	76	Squamous	Distal	Locally advanced	Palliative	–/–
Sarbia (98)	2012	M	69	Adenocarcinoma	OGJ	Metastatic	Chemo	–/–
Sign of Leser-Trélat								
Chiba (99)	1996	F	79	Squamous	–	Locally advanced	Chemo/RT	8 months/dead
Wieland (100)	2008	M	59	Adenocarcinoma	–	Metastatic	–	–/–
Gaduputi (101)	2014	M	65	Squamous	Distal	Locally advanced	Chemo/RT	–/–
SCLE								
Jasim (102)	2007	M	66	Adenocarcinoma	OGJ	Early stage	Surgery	–/alive
Koritala (103)	2015	M	59	Squamous	Distal	Metastatic	Chemo	–/dead
Xie (104)	2020	M	77	–	–	Locally advanced	Palliative	–/dead
PNP								
Arranz (105)	2005	F	63	Squamous	–	Metastatic	Chemo	5 months/dead
Cho (106)	2013	M	68	Squamous	Mid	Metastatic	Chemo	<1 months/dead
Jayachandran (107)	2017	M	52	Squamous	–	–	Surgery	–/–

Table 3 (continued)

Table 3 (continued)

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival
Melanotic macules								
Eng (108)	1991	M	64	Adenocarcinoma	Distal	Metastatic	RT	10 months/dead
Busam (109)	2003	M	64	Adenocarcinoma	Distal	Metastatic	Chemo	12 months/dead
Anti-laminin γ 1-pemphigoid								
Goetze (110)	2017	M	42	Adenocarcinoma	Distal	Metastatic	Chemo	4 months/dead
Sweet's syndrome								
Sobol (111)	2009	M	62	Adenocarcinoma	Distal	Locally advanced	Chemo/RT/surgery	--/dead
Disseminated superficial porokeratosis								
Lee (112)	2010	M	82	-	-	-	Surgery	-/-
Interstitial granulomatous dermatitis								
Moyano Almagro (113)	2013	M	67	Squamous	Proximal	-	RT/Chemo	12 months/dead
Erythema gyratum repens								
Matta (114)	2020	M	61	Squamous	-	-	Chemo	-/-
Lichenoid dermatosis								
Kato (115)	2011	M	84	Squamous	-	Early stage	RT	-/-

F, female; Mid, middle third of esophagus; M, male; Distal, distal third of esophagus; RT, radiotherapy; Proximal, proximal third of esophagus; Chemo, chemotherapy; AN, acanthosis nigricans; OGJ, esophagogastric junction; SCLE, subacute cutaneous lupus erythematosus; PNP, paraneoplastic pemphigus.

symptoms of the underlying malignancy, however, this pattern is not universal (125), and among patients with esophageal cancer, two cases are reported in which skin manifestations preceded the onset of symptoms of malignancy (97,98).

Treatment of malignant acanthosis is with management of the underlying malignancy (126), generally resulting in regression of the AN (96). Recurrence of AN has been described as indicating recurrence or metastasis of the underlying malignancy (125).

Sign of Leser-Trélat

The sign of Leser-Trélat is characterised by the rapid development of numerous seborrheic keratoses (101). Seborrheic keratoses are hyperpigmented, well-demarcated skin lesions with a characteristic “stuck-on” appearance, often occurring in a “raindrop” pattern (101) on the trunk and extremities, however they may also occur on the face and neck (127). The sign has been reported in association with a variety of underlying malignancies, predominantly adenocarcinomas of the gastrointestinal tract (101). Regression of lesions has been reported following definitive treatment of the underlying malignancy in approximately 50% of cases (101,127).

The pathophysiological mechanism for the sign is not well established (128). Multiple histologic variants of seborrheic keratosis exist; most common among these is the acanthotic subtype, which is characterised by keratinocyte proliferation (129).

Three cases are reported in association with esophageal carcinoma. In a typical case, Gaduputi *et al.* (101) described the sign of Leser-Trélat occurring in a patient with SCC of the esophagus. Treatment with chemoradiotherapy resulted in macroscopic tumor shrinkage, without regression of the lesions.

Subacute lupus erythematosus

Malignancy-associated subacute cutaneous lupus erythematosus (SCLE) is rare (104). The condition is characterised by a papulosquamous or annular rash, most commonly affecting photodistributed areas (103,130), with variable systemic manifestations, often including arthralgia. Anti-Ro/SSA antibodies are typically present. SCLE lesions are characterised by hyperkeratosis and follicular plugging. Perivascular and appendageal lymphocytic infiltrates tend to be more superficial, differentiating the condition from discoid lupus erythematosus (103).

All reported cases of SCLE reported in association

with esophageal cancer responded to treatment of the underlying tumor, with adjunctive use of oral steroids and hydroxychloroquine shown to be beneficial where described (102,104).

Paraneoplastic pemphigus (PNP)

PNP is an erosive mucocutaneous bullous syndrome most commonly associated with lymphoproliferative disorders (6), and rarely with solid tumors (131). Diagnostic criteria (132) emphasize a combination of major and minor histopathological and clinical findings, which include progressive ulcerative mucosal lesions, and polymorphous, desquamative skin lesions.

PNP occurs as a consequence of cross-reactivity between tumor-directed autoantibodies and epidermal proteins, including desmoplakin, which play a role in epidermal cell adhesion (107). PNP has a poor prognosis and a high mortality rate (133), frequently as a result of erosive skin disease rather than the malignancy itself (132).

The treatment of PNP is not well established, and the condition is, in many cases, treatment refractory (132). Management includes treatment of the underlying malignancy as well as high dose steroids (132). Other agents including azathioprine, cyclosporin, rituximab and intravenous immunoglobulin have also been used with variable success (133-135).

Other paraneoplastic dermatological syndromes

Individual case reports exist for other paraneoplastic dermatoses occurring in association with esophageal cancer, namely: anti-laminin γ 1-pemphigoid (110), Sweet's syndrome (111), disseminated superficial porokeratosis (112), granulomatous dermatitis (113), erythema gyratum repens (114), lichenoid dermatosis (115), and two cases of eruptive melanotic macules in a distribution mimicking that of Peutz-Jeghers syndrome (108,109).

Paraneoplastic rheumatological syndromes (Table 4)

Hypertrophic osteoarthropathy (HOA)

By far, the predominant paraneoplastic rheumatological condition reported in association with esophageal cancer is HOA, previously termed hypertrophic pulmonary osteoarthropathy or HPOA (154), given its frequent association with pulmonary disorders (155). HOA was first described in association with esophageal cancer in 1959 by Peyman (156). Since then, twenty cases of HOA associated with esophageal cancers have been reported in

Table 4 Paraneoplastic rheumatological syndromes

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival
HOA								
Ullal (136)	1972	M	49	Leiomyoma	Distal	Locally advanced	Surgery	12 months/alive
Carroll (137)	1974	F	78	Adenocarcinoma	Mid	-	Palliative	-/dead
Barber (138)	1983	F	54	Squamous	Distal	-	Surgery	6 months/dead
Polkey (139)	1991	F	71	Adenocarcinoma	Distal	Locally advanced	Palliative	1.5 months/dead
Morita (140)	2003	M	65	Squamous	Distal	Locally advanced	Surgery/RT/Chemo	36 months/alive
Wechalekar (141)	2011	M	59	Adenocarcinoma	Distal	Locally advanced	RT/Chemo/surgery	7 months/alive
Murosaki (142)	2015	M	58	Squamous	-	-	Palliative	-/-
Saif (143)	2016	M	38	Neuroendocrine	Distal	Locally advanced	Surgery/RT/Chemo	72 months/alive
DM								
Karp (144)	1985	M	63	Squamous	Distal	-	RT	10 months/dead
Tanabe (145)	2001	F	78	Adenocarcinoma	Distal	Metastatic	Palliative	3 months/dead
Ifikhar (146)	2006	M	58	Adenocarcinoma	-	Locally advanced	-	-/-
Kikuchi (147)	2008	M	62	Squamous	-	Locally advanced	Surgery/RT/Chemo	96 months/alive
Harrison (148)	2008	M	58	Adenocarcinoma	-	Metastatic	RT/Chemo	2 months/dead
Terada (149)	2013	M	71	Signet ring carcinoma	Distal	-	-	9 months/dead
Laidler (150)	2018	M	69	Adenocarcinoma	Distal	Early stage	Surgery	9 months/alive
Subhash (151)	2020	M	45	Poorly differentiated	OGJ	Locally advanced	-	-/-
HMGCR antibody-associated myopathy								
Tsujikawa (152)	2016	M	59	Small cell	-	Locally advanced	Surgery/Chemo	10 months/dead
Polymyalgia rheumatica-like syndrome								
Umetsu (153)	2019	F	70	Squamous	Mid	Early stage	Surgery	-/-

HOA, hypertrophic osteoarthropathy; M, male; Distal, distal third of esophagus; F, female; Mid, middle third of esophagus; RT, radiotherapy; Chemo, chemotherapy; DM, dermatomyositis; OGJ, esophagogastric junction; HMGCR, β -Hydroxy β -methylglutaryl-CoA reductase.

the literature, including two case series of seven and five cases respectively (157,158), and eight further case reports (136-143).

HOA is characterised by fingernail clubbing, proliferative periostitis, particularly of tubular bones, and collagen deposition, leading to erythema, arthralgia, and synovial effusions of the large joint spaces (159). The pathogenesis of HOA is debated and may vary depending on clinical context, but likely results as a consequence of tumor secretion of growth factors such as prostaglandin E and cytokines such as fibroblast growth factor (160). Other proposed mechanisms include interaction between megakaryocytes and endothelium (161), as well as hormonal (162), and neurologic (163) etiologies.

Where associated with esophageal cancers, and where surgical resection of the primary tumor has been feasible, this has led in all reported cases to rapid and complete resolution of symptoms (136,138,140,141). Clinical benefit has been reported with the use of bisphosphonates (164,165), and octreotide (166), both of which have anti-VEGF properties which may account for their efficacy in this setting. Symptomatic management with conventional NSAIDs and opiates yields variable response (158).

Dermatomyositis (DM)

DM is an idiopathic inflammatory myopathy characterised by progressive proximal skeletal muscle weakness, myocyte inflammation, and pathognomic cutaneous lesions which include a periorbital or heliotrope rash and Gottron's sign (167), as well as a photosensitive poikilodermatous rash on sun-exposed areas (148). The prevalence of malignancy in adults diagnosed with DM is debated, but has been reported as between 20–30% (144,148,150,168). Although DM affects women 2 to 3 times more frequently than men (169), almost all case reports of DM associated with esophageal carcinoma have been reported in men.

EULAR/ACR criteria for idiopathic inflammatory myopathies (170) assist in the diagnosis of DM and require both clinical and laboratory assessment, including anti-Jo-1 autoantibody, CK and LDH; and muscle biopsy. CK levels may be useful in tracking disease response to cancer-directed therapy (6). Among patients with esophageal cancer, CK was typically elevated (144-146,148,151). Autoantibodies were negative in two thirds of cases (145,149-151).

Steroids are the mainstay of treatment in the cases reported (144-146,148), with rapid response to therapy noted in the majority of reported cases. Harrison *et al.* (148)

described a case where IVIG was used following the failure of high dose dexamethasone; unfortunately providing no benefit in a rapidly progressive case. Rare presentations include a case of amyopathic DM (147) as well as a case associated with adenocarcinoma neuroendocrine differentiation resulting in tumoral PTHrP secretion (145).

Other paraneoplastic rheumatological syndromes

Other rheumatological syndromes reported in association with esophageal cancers are outlined in *Table 4*, and include a case of β -Hydroxy β -methylglutaryl-CoA reductase (HMGCR) antibody-associated myopathy (152). Umetsu *et al.* (153) reported a case of esophageal cancer occurring in association with a polymyalgia rheumatica-like clinical syndrome with radiological characteristics of this seen on PET-CT.

Paraneoplastic renal syndromes (*Table 5*)

Overview

Glomerulopathies refer to diseases characterised by renal glomerular injury. The most common malignancies associated with paraneoplastic glomerular injury are Hodgkin's lymphoma and carcinomas of the lung and gastrointestinal tract (185). Multiple discrete glomerular pathologies have been described in association with malignancy, the most common among patients with solid tumors being membranous nephropathy (MN) (178). Paraneoplastic renal syndromes which have been described in association with esophageal cancer are summarized in *Table 5*.

Criteria for the diagnosis of paraneoplastic glomerulopathy have been established by Bacchetta *et al.* (186), and emphasise (I) the temporal association between the diagnosis of glomerulopathy and malignancy, (II) clinical improvement of the nephropathy with effective cancer-directed therapy, (III) deterioration associated with recurrence of malignancy, and (IV) the absence obvious alternate etiology, in the diagnosis of these conditions.

MN

MN is the most common glomerulonephritis associated with malignancy (178). The incidence of malignancy in patients with MN varies, with estimates of 1.4–13% across multiple case series of undifferentiated solid tumors (178,187,188). Histologically, the condition is characterised by basement membrane thickening and subepithelial immune complex deposition within the glomeruli (189).

Table 5 Paraneoplastic renal syndromes

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival
IgA nephropathy								
Beaufils (171)	1985	F	75	Squamous	–	Metastatic	–	–
Lam (172)	1998	M	70	Squamous	Mid	Early stage	Surgery	–/alive
MCD								
Yoshida (173)	1979	M	50	Squamous	–	–	Steroids	3 months/dead
Uezono (174)	1989	M	68	Squamous	–	Early stage	Surgery	–
Gallego (175)	1994	M	64	Squamous	Mid	Locally advanced	Palliative	1 months/dead
MN								
Heckerling (176)	1985	M	65	Squamous	Mid	Locally advanced	Surgery/RT/Chemo	–/alive
Suzuki (177)	1991	M	65	Squamous	–	–	Surgery	3 months/dead
Burstein (178)	1993	M	65	–	–	–	–	21 months/dead
Yedidag (179)	1997	M	61	Squamous	–	–	Steroids	9 months/dead
Muramoto (180)	2009	M	54	Squamous	Distal	Locally advanced	RT/EMR	–/alive
Ito (181)	2013	M	73	Squamous	Distal	Early stage	Surgery	18 months/alive
MPGN								
Walker (182)	1981	F	59	Squamous	Mid	–	Surgery	24 months/alive
Nagasaka (183)	1999	M	76	Squamous	–	–	Surgery	–
Nephrotic syndrome (renal lesion not described)								
Naritaka (184)	2010	M	78	Squamous	Mid	Locally advanced	Surgery	12 months/alive

IgA, immunoglobulin A; F, female; M, male; Mid, middle third of esophagus; MCD, minimal change disease; MN, membranous nephropathy; RT, radiotherapy; Chemo, chemotherapy; Distal, distal third of esophagus; EMR, endoscopic mucosal resection; MPGN, membranoproliferative glomerulonephritis.

Paraneoplastic MN is associated with a relatively higher number of pro-inflammatory cells in glomeruli compared to primary MN (188), indicating an enhanced immune reaction as a possible mechanism for glomerular injury.

In the paraneoplastic setting, glomerular deposition of cancer-associated immune complexes such as carcinoembryonic antigen (190), prostate-specific antigen (191), and melanoma antigens (192) has been reported. Specifically to esophageal cancer, two case reports have hypothesised a link between serum SCC antigen and development of MN, with both cases demonstrating a link between serum SCC antigen levels and degree of proteinuria (180,181).

Paraneoplastic MN associated with esophageal cancer has been reported six times in the literature (176–181). In a typical case, Ito *et al.* (181) described a 73-year-old male who presented with lower limb edema and proteinuria.

Following diagnosis of MN, he was screened for malignancy and diagnosed with early-stage esophageal SCC. Subtotal esophagectomy resulted in resolution of proteinuria.

Immunoglobulin A (IgA) nephropathy/Berger's disease

IgA nephropathy is characterised histologically by deposition of IgA within the renal mesangium. Although commonly a disease of childhood, development of IgA nephropathy in older patients is more likely to be related to malignancy (193). Clinically, the condition is characterised by recurrent episodes of macroscopic haematuria with persistent microscopic haematuria and/or proteinuria. Rarely it can present as a nephrotic syndrome or acute renal failure (194). The pathophysiology of paraneoplastic IgA nephropathy is poorly understood, however it has been hypothesised that invasion of the gastrointestinal mucosa by tumor leads to increased circulating IgA levels and

consequent deposition within the glomeruli (193), resulting in the release of cytokines and oxygen free radicals which induce inflammation, and ultimately fibrosis.

IgA nephropathy associated with esophageal carcinoma has been reported twice in the literature (171,172). Lam *et al.* (172) reported a case of a 70-year-old male who presented with a pruritic rash, microscopic haematuria and proteinuria; 22 months later he was diagnosed with early stage mid-esophageal SCC. The other reported case is of a 74-year-old female with metastatic esophageal squamous cancer diagnosed with IgA nephropathy at autopsy (171).

Minimal change disease (MCD)

MCD typically presents with nephrotic syndrome. In the adult population, it constitutes approximately 15% of idiopathic nephrotic syndromes, with a male preponderance (195). The pathogenesis of MCD is thought to be related to dysfunctional T-cell regulation and function leading to podocyte injury and fusion of podocyte foot processes (196). Corticosteroids are considered to be the standard of care first-line therapy for MCD (195).

Three cases of MCD in association with esophageal carcinoma have been reported in the literature (173-175). In a typical case, Gallego *et al.* (175) describe a 64-year-old male who presented with progressive dysphagia and weight loss, as well as generalised edema. He was found to have significant proteinuria associated with hypoalbuminemia, and was later diagnosed with metastatic esophageal cancer. Autopsy confirmed the presence of MCD.

Membranoproliferative glomerulonephritis (MPGN)

MPGN, also known as mesangiocapillary glomerulonephritis, is a progressive glomerulopathy characterized histologically by mesangial hypercellularity, endocapillary proliferation, and thickening of the capillary wall (197). The clinical presentation and course are both highly variable. Patients may present asymptotically with microscopic haematuria or proteinuria, symptomatically with acute nephritic or nephrotic syndromes, or acutely unwell with rapidly progressive glomerulonephritis (197).

Paraneoplastic MPGN is more commonly reported in association with haematological malignancies, however there are case reports associated with solid tumors including small cell lung cancer (198), gastric cancer (199), colorectal cancer (200), transitional cell carcinoma (201), renal cell carcinoma (202), prostate cancer (203) and esophageal cancer (182,183). The pathogenesis of paraneoplastic MPGN is not well understood, but has been hypothesized

to occur as a consequence of immune-complex deposition in the kidneys secondary to an ineffective host immune response to tumor antigens (202).

Treatment of the underlying cancer has led to improved renal outcomes in various reported cases of paraneoplastic MPGN (201,202). However, where definitive treatment of malignancy was not possible, there have been reported cases of therapeutic response to corticosteroids (200,203).

There have been two reported cases of MPGN associated with esophageal cancer (182,183). Walker *et al.* (182) reported a case of a 74-year-old female who presented with a 5-week history of bilateral lower limb oedema and proteinuria 7 weeks post esophagectomy for mid-esophageal SCC. Renal biopsy confirmed the presence of MPGN.

Paraneoplastic endocrine syndromes (Table 6)

Overview

Paraneoplastic syndromes may arise as a consequence of tumoral production and secretion of physiologically active hormones or peptides, resulting in abnormal endocrine or metabolic function with loss of physiological feedback autoregulation. Criteria for diagnosis of paraneoplastic endocrine syndromes have been proposed by Dimitriadis *et al.* (218), and emphasise both temporal-clinical associations with underlying malignancy and anti-cancer therapy, as well as detectability of immunoreactive hormone and hormonal mRNA within tumoral tissue.

Reports of endocrine paraneoplastic syndromes occurring in association with esophageal cancer are rare (Table 6), and principally relate to syndrome of inappropriate antidiuretic hormone secretion (SIADH) and humoral hypercalcemia of malignancy (HHM) related to PTHrP secretion. Although reported as paraneoplastic phenomena in other cancer types (218,219), we found no detailed reports of acromegaly, hyperprolactinaemia, hyperthyroidism, or of hypoglycaemia directly attributable to esophageal cancer in the literature.

Hypercalcemia

Hypercalcemia among patients with esophageal cancer is common, with one retrospective series (220) reporting an incidence of 27.6% at any timepoint during treatment among an unselected patient population encompassing all stages of disease. All patients who developed hypercalcaemia had either squamous or adenosquamous histology; the prevalence of hypercalcemia was not explained by bony metastatic disease, which was present in only 15% of those with hypercalcemia. Another series (221)

Table 6 Paraneoplastic endocrine syndromes

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival
PTHrP secreting tumors								
Fernández-Real (204)	1994	M	56	Squamous	Distal	Metastatic	Surgery	–/dead
Nozu (205)	1995	M	68	Undifferentiated	OGJ	Metastatic	Chemo	5 months/dead
Nagashima (206)	1999	M	47	Small cell/squamous	Mid	Metastatic	Chemo/RT	7 months/dead
Watanabe (207)	1999	M	66	Squamous	Mid	Metastatic	Palliative	1 months/dead
Watanabe (207)	1999	F	81	Squamous	Mid	Metastatic	Palliative	<1 months/dead
Tanabe (145)	2001	F	78	Adenocarcinoma	Distal	Metastatic	Palliative	3 months/dead
Fereidooni (208)	2003	M	63	Small cell/squamous	–	Metastatic	Palliative	<1 months/dead
Nakata (209)	2006	M	56	Squamous	Distal	Locally advanced	Surgery/RT/Chemo	16 months/alive
Kanno (210)	2007	F	60	Small cell	Distal	Metastatic	Chemo	16 months/dead
SIADH								
Doherty (211)	1984	F	74	Small cell	Distal	Locally advanced	RT	–/dead
Heyes (212)	1985	F	53	Small cell	Mid	Locally advanced	Chemo/RT	2 months/dead
Naruki (213)	1986	M	67	Small cell	–	Metastatic	RT	10 months/dead
Komura (214)	2001	M	62	Small cell	–	Metastatic	Chemo	11 months/dead
Kanzaki (215)	2010	M	66	Small cell	–	Locally advanced	Chemo/RT	16 months/alive
Suzuki (216)	2010	M	63	Small cell	–	Metastatic	Chemo	–/dead
Ando (217)	2011	M	54	Small cell	Distal	Locally advanced	Surgery/Chemo	9 months/dead

PTHrP, parathyroid hormone related peptide; M, male; Distal, distal third of esophagus; OGJ, esophagogastric junction; Chemo, chemotherapy; Mid, middle third of esophagus; RT, radiotherapy; F, female; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

reported a prevalence of 7.7% among operatively managed patients with esophageal SCC. Other series which included patients with all disease stages, have reported comparable survival among patients with hypercalcemia and those without (220,222).

In the context of malignancy, hypercalcemia is a common endpoint of at least four distinct pathophysiological pathways, namely secretion of PTHrP, PTH, and calcitriol, as well as local osteolysis (223). Clinically, hypercalcemia may present with neurological features including fatigue, aesthaenia, confusion, personality change, and coma; GI disturbance, including nausea, vomiting, constipation, and (rarely) pancreatitis; renal impairment or failure; nephrogenic diabetes insipidus, cardiac arrhythmias, and other systemic symptoms including anorexia, polydipsia/polyuria and bony pain. The degree of symptomatology depends not only on the extent of hypercalcemia but also on the acuity with which it has developed (224).

Treatment of hypercalcemia is with two principal mechanistic goals in mind, namely restoration of renal calciuresis, and inhibition of osteoclastic activity (224). Acute management includes fluid resuscitation, which both corrects dehydration, and promotes calciuresis. The use of loop diuretics is not supported by a strong evidence base (224), but may be used as an adjunct once euolemia and adequate urine output has been established in the acute setting (6). Bisphosphonates, including pamidronate and zoledronate, are widely used to treat HHM, and their use is supported by a robust evidence base (226-228). Correction of hypercalcaemia may take many days to achieve; levels typically nadir between 4–7 days after administration of bisphosphonates, and response is typically durable for up to 4 weeks (228). Calcitonin, which both inhibits osteoclastic activity and renal calcium reabsorption, may be used in the acute setting and has both a more rapid onset and a more modest efficacy than bisphosphonates (6). Long-term use of

calcitonin is usually ineffectual due to tachyphylaxis (224), although its efficacy may be extended where co-administered with glucocorticoids (229).

SIADH

The SIADH, is characterised by hypoosmotic, euvolaemic hyponatraemia accompanied by urinary hyperosmolality/hyponatremia, in the absence of other precipitating causes such as heart failure, cirrhosis, renal or adrenal insufficiency, thyroid dysfunction or diuretic use (230). Paraneoplastic SIADH arises due to tumoral secretion of both anti-diuretic hormone (ADH) and atrial natriuretic hormone (ANP), leading to increased expression of renal tubular aquaporins with resultant free water reabsorption and natriuresis (6).

Classically, SIADH has been associated with small cell lung cancer, which accounts for approximately 70% of paraneoplastic SIADH (230). The symptoms of SIADH-associated hyponatremia depend on the acuity of onset (231) as well as the degree of hyponatraemia, and include confusion, memory loss, fatigue, headache, nausea, and coma/death in severe cases (232).

Treatment strategies are based predominantly on expert opinion (233,234), but should in the first instance aim to address the underlying malignancy. In severe (serum sodium concentration <125 mmol/L, or symptomatic) cases, correctional treatment is indicated. Where no clinical contraindications exist, initial management of asymptomatic SIADH typically involves instituting fluid restriction of 1L/day; this in itself may correct the hyponatraemia within a number of days. In life-threatening cases, hypertonic saline may be administered, aiming to increase serum sodium by no more than 8–10 mmol/L over 24 hours (232,235). Pharmacological treatments of SIADH include demeclocycline, a tetracycline derivative, which inhibits the action of ADH at the renal tubule, leading to loss of free water with resultant correction of hyponatraemia (234), and ADH-receptor antagonists, such as tolvaptan and conivaptan.

Other paraneoplastic endocrine syndromes

Although ACTH (236-240), gastrin (241), and calcitonin (238,240) synthesis have been reported as laboratory findings in association with esophageal small cell carcinomas, their clinical significance remains uncertain, and case series which document production of these hormones report this as a histopathological finding of importance for diagnostic discrimination, rather than one which resulted in clinical sequelae.

A single case of apparent paraneoplastic Cushing's syndrome occurring in association with esophageal small cell carcinoma has been reported (242). Although biochemical and clinical features suggestive of Cushing's syndrome were present in this case, serum ACTH was normal.

Paraneoplastic haematological syndromes (Table 7)

Granulocyte colony stimulating factor (GCSF) secretion

GCSF is a glycoprotein hormone, typically produced in vascular endothelial cells, fibroblasts, and macrophages. GCSF stimulates production, differentiation, and function of neutrophil precursors (280). Secretion of GCSF by tumors has been reported in lung (281), liver (282), and gastric (283) cancers, and, although rare, is well described in association with esophageal squamous cell and carcinosarcoma histologies, with 36 reported cases in the English language literature, the majority of which are from Japan.

GCSF producing tumors may display autocrine and paracrine growth activity via the *JAK2/STAT3* pathways, resulting in proliferation and migration of tumor cells, and a consequently aggressive phenotype (284-286). Proposed mechanisms of GCSF production include mutations in *RAS* oncogene mutations which result in overexpression of GCSF mRNA (287); rearrangements of the *GCSF* gene (288); amplification of the *GCSF* gene leading to constitutive GCSF overproduction (289), and amplification/activation of binding factors which target the regulatory or promoter regions of the *GCSF* gene (290).

In contrast to leukaemic malignancies, high levels of circulating mature neutrophils as a consequence of paraneoplastic GCSF secretion typically does not appear to result in vasoocclusion or hyperviscosity syndromes, and does not require specific therapy (6). Co-secretion of other cytokines with GCSF is common. Of the 36 reported cases of GCSF secreting tumor, five reported co-secretion of IL-6 (243,253,257,263,268); while two reported co-secretion of PTHrP (206,209).

Thrombocytosis

Malignancy-associated thrombocytosis is an established marker of poor prognosis in a number of cancers (291-293), including esophageal cancer (294-296). Although the precise pathophysiological mechanisms of paraneoplastic thrombocytosis remain unclear,

Table 7 Paraneoplastic haematological syndromes

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival
GSCF secreting tumors								
Ota** (243)	1998	M	63	Carcinosarcoma	Mid	Early stage	Surgery	-/-
Watanabe (207)	1999	F	81	Squamous	Mid	Metastatic	Palliative	<1 month/dead
Oshiro (244)	1999	M	56	Carcinosarcoma	-	Early stage	Surgery	8 months/alive
Nagashima ^Δ (206)	1999	M	47	Small cell/squamous	Mid	Metastatic	Chemo/RT	7 months/dead
Ichiishi (245)	2000	M	66	Squamous	Distal	-	Palliative	2 months/dead
Matsumoto (246)	2000	M	66	Squamous	Distal	Metastatic	Surgery/RT/Chemo	16 months/dead
Asai (247)	2003	M	60	Carcinosarcoma	-	-	Surgery/Chemo	-/-
Fujimori (248)	2003	M	76	Carcinosarcoma	Distal	Early stage	Surgery	-/-
Nakata ^Δ (209)	2006	M	56	Squamous	Distal	Locally advanced	Surgery/RT/Chemo	16 months/alive
Maejima (249)	2007	M	80	Carcinosarcoma	Distal	Metastatic	Palliative	4 months/dead
Sasaki (250)	2007	M	62	Carcinosarcoma	Distal	Locally advanced	Surgery/Chemo	5 months/dead
Miyamoto (251)	2008	M	51	Carcinosarcoma	Mid	Locally advanced	Surgery/Chemo	23 months/alive
Unno (252)	2008	M	63	Squamous	-	Locally advanced	RT/Chemo	-/-
Mimatsu** (253)	2008	M	69	Squamous	Mid	Metastatic	RT	7 months/dead
Miki (254)	2009	M	58	Squamous	Mid	Metastatic	Chemo	-/dead
Tanabe (255)	2009	M	76	Squamous	Distal	Locally advanced	Surgery/RT/Chemo	10 months/dead
Ito (256)	2010	M	70	Carcinosarcoma	Distal	Early stage	Surgery	60 months/alive
Tamura** (257)	2011	M	47	Carcinosarcoma	Distal	Early stage	Surgery	16 months/alive
Eto (258)	2013	M	59	Squamous	Distal	Locally advanced	Surgery/Chemo	13 months/alive
Eto (258)	2013	M	58	Squamous	Distal	Locally advanced	Chemo/surgery	17 months/alive
Eto (258)	2013	M	75	Squamous	OGJ	Metastatic	Chemo	3 months/alive
Mayanagi (259)	2013	M	30	Squamous	Proximal	Locally advanced	Surgery/RT/Chemo	3 months/alive
Shimakawa (260)	2014	M	70	Squamous	Distal	Locally advanced	Surgery/Chemo	12 months/dead
Kobayashi (261)	2015	M	69	Carcinosarcoma	Proximal	Early stage	Surgery/Chemo	60 months/alive
Hagiwara (262)	2015	M	63	Squamous	Distal	Locally advanced	Surgery	4 months/dead
Oshikiri** (263)	2015	M	65	Squamous	Distal	Locally advanced	Surgery	3 months/alive
Kitani (264)	2016	F	92	Squamous	Distal	Locally advanced	Surgery	18 months/alive
Fukuda (265)	2017	M	50	Squamous	Distal	Metastatic	RT/Chemo	3 months/dead
Yamaguchi (266)	2017	M	66	Squamous	Distal	Locally advanced	Palliative	3 months/dead
Hoshimoto (267)	2018	F	72	Adenocarcinoma	OGJ	Locally advanced	Surgery/Chemo	38 months/alive
Shioga** (268)	2018	M	51	Carcinosarcoma	Mid	Locally advanced	Surgery/Chemo/RT	7 months/alive
Tochimoto (269)	2018	M	42	Squamous	Distal	Locally advanced	Surgery/Chemo	-/-
Jayarangaiah (270)	2019	F	72	Squamous	Distal	-	Palliative	2 months/dead

Table 7 (continued)

Table 7 (continued)

Author	Year	Gender	Age	Histology	Site	Stage	Treatment	Survival
Yu (271)	2019	M	74	Adenocarcinoma	Distal	Locally advanced	Surgery/Chemo	6 months/alive
Chang (272)	2020	F	72	Adenocarcinoma	OGJ	Locally advanced	Chemo	–/–
Azzam (273)	2020	M	51	Squamous	OGJ	Locally advanced	Surgery/Chemo	84 months/alive
Acquired factor V inhibitor								
Ahmadinejad (274)	2013	M	82	Squamous	Mid	–	RT	–/dead
Henoch-Schönlein purpura								
Weiler-Bisig (275)	2005	–	–	–	–	–	–	–
Chen (276)	2020	M	60	Squamous	Distal	Early stage	Surgery	12 months/alive
Idiopathic thrombocytopenia purpura								
Shutt (277)	2004	F	72	Squamous	Mid	Locally advanced	RT	3 months/dead
Disseminated intravascular coagulation								
Sasaki (278)	2013	F	70	–	–	Locally advanced	Chemo/RT	–/–
Amatatsu (279)	2015	M	66	–	–	Early stage	Chemo	–/–

**₂, co-secretion with IL-6; ^Δ, co-secretion with PTHrP. GCSF, granulocyte colony stimulating factor; M, male; Mid, middle third of esophagus; F, female; Chemo, chemotherapy; RT, radiotherapy; Distal, distal third of esophagus; OGJ, esophagogastric junction; Proximal, proximal third of esophagus; IL-6, interleukin-6; PTHrP, parathyroid hormone related peptide.

it may result as a consequence of tumor-derived IL-6 stimulation of platelet production (295). Activated platelets are known to produce a number of cytokines capable of inducing angiogenesis (295). The prevalence of thrombocytosis is reported as between 2.4% and 50% (294–297) in patients with esophageal cancer. Where described, most series report an association between thrombocytosis and poor prognosis (294–296).

Other paraneoplastic haematological syndromes

Other paraneoplastic haematological syndromes reported in association with esophageal cancers are summarised in Table 7, and include a case of acquired factor V inhibitor in an elderly male patient presenting with dysphagia, epistaxis, and melena. Administration of prednisolone resulted in reversal of the coagulopathy; OGD confirmed a diagnosis of esophageal SCC (274). Further cases include reports of steroid-responsive Henoch-Schönlein purpura (275,276), and of idiopathic thrombocytopenia purpura which initially responded to intravenous immunoglobulin, but which ultimately progressed to fatal gastrointestinal

and intrapulmonary haemorrhage (277). No cases of DIC directly attributable to esophageal cancer have been reported, although two reports describe DIC occurring in patients with esophageal cancer. In both cases, DIC occurred in the context of severe sepsis rather than as a directly attributable consequence of the underlying malignancy (278,279).

Conclusions

This review collates and summarises the literature regarding paraneoplastic syndromes reported in association with esophageal cancer, and serves as a reference for clinicians. Although rare, a wide spectrum of paraneoplastic syndromes are reported in association with esophageal cancer. Many paraneoplastic syndromes are clearly defined and have well established and effective treatments. Timely recognition of these syndromes and their potential association with underlying malignancy should prompt clinicians to undertake a broad search for underlying malignancy.

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Footnote

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