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REVIEW

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease

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Abstract. Sørensen JB, Andersen MK, Hansen HH (Department of Oncology, Finsen Centre, National University Hospital/Rigshospitalet, Copenhagen, Denmark). Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease (Review). *J Intern Med* 1995; **238**: 97–110.

The first clinical case of a patient with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was presented by Schwartz *et al.* in 1957 (*Am J Med* 1957; **23**: 529–42), describing two patients with lung cancer who developed hyponatraemia associated with continued urinary sodium loss. They postulated that the tumours led to the inappropriate release of antidiuretic hormone (ADH), later discovered to consist of arginine-vasopressin (AVP). This suggestion was later confirmed in several studies. The clinical description of the syndrome has changed little since the original observation, and the cardinal findings of SIADH are as follows: (i) hyponatraemia with corresponding hypo-osmolality of the serum and extracellular fluid, (ii) continued renal excretion of sodium, (iii) absence of clinical evidence of fluid volume depletion, (iv) osmolality of the urine greater than that appropriate for the concomittant osmolality of the plasma, i.e. urine less than maximal diluted, and (v) normal function of kidneys, suprarenal glands and thyroid glands. Measurement of AVP in plasma is not a part of the definition of SIADH. SIADH may be caused by a variety of malignant tumours, but may also be caused by various other conditions, such as disorders involving the central nervous system, intrathoratic disorders such as infections, positive pressure ventilation and conditions with decrease in left atrial pressure. Also, a large number of pharmaceutical agents have been shown to produce SIADH, including a number of cytotoxic drugs such as vincristine, vinblastine, cisplatin, cyclophosphamide, and melphalan.

A broad spectrum of malignant tumours has been reported to cause SIADH; however, most of these observations have been in case reports including very few patients. This includes a number of primary brain tumours, haematologic malignancies, intrathoracic non-pulmonary cancers, skin tumours, gastrointestinal cancers, gynaecological cancer, breast-and prostatic cancer, and sarcomas. Larger series of patients have revealed that SIADH occurs in 3% of patients with head and neck cancer (47 cases out of 1696 patients), in 0.7% of patients with non-small-cell lung cancer (three cases out of 427 patients), and in 15% of cases of small-cell lung cancer (214 cases out of 1473 patients). The optimal therapy for SIADH is to treat the underlying malignant disease. If this is not possible, or if the disease has become refractory, other treatment methods are available such as water restriction, demeclocycline therapy, or, in severe cases, infusion of hypertonic saline together with furosemide during careful monitoring.

Introduction

In 1928, the first case of a patient with a hormonally induced paraneoplastic syndrome was reported by Brown [1] who described an ectopically induced adrenal hyperplasia later known to be caused by ACTH produced by tumour cells. Since this initial paper, other paraendocrine syndromes have been described, amongst them the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The first clinical cases were presented by Schwartz *et al.* [2] in 1957, who described two patients with lung cancer who developed hyponatraemia associated with continued urinary sodium loss. They noted that the syndrome was similar to what occurred when normal individuals were given antidiuretic hormone (ADH). They postulated that the tumours led to the inappropriate release of ADH, later discovered to consist of arginine-vasopressin (AVP). In this paper [2], as well as in a second publication by Bartter & Schwartz 10 years later [3], and in a publication by Bartter in 1973 [4], the syndrome of SIADH was further described. In 1963, Amatruda *et al.* [5] were able to demonstrate that SIADH in patients with small-cell lung cancer was, in fact, caused by ectopic tumour production of AVP. Subsequently, the observation of the absence of inappropriate elevated AVP levels in a few cases that otherwise satisfy all clinical criteria for SIADH has led to the use of the term SIAD, the syndrome of inappropriate antidiuresis, as a more general description of this disorder. Although many causes of SIAD have been described, malignancies and, in particular, small-cell carcinomas of the lung, should always be considered in the differential diagnosis of these patients.

The clinical description of the syndrome has changed little since the original observation by Schwartz *et al.* [2], but much more knowledge has accumulated about the production of AVP and related peptides. This review will highlight the current knowledge of the pathophysiology of SIADH in malignant disease, together with a description of the occurrence in different tumour types, the clinical behaviour and prognostic impact, together with a review on the various treatment possibilities.

Definition

The cardinal feature of SIADH is hyponatraemia. In the original paper by Schwartz *et al.* [2], the two patients also had hypo-osmolality of the extracellular fluid and a urine persistently hypertonic to the plasma. Renal and adrenal cortical functions were normal. AVP was not measured but postulated to be secreted at a sustained and inappropriate level. Inappropriate secretion is defined as secretion that continues in face of hypotonicity of plasma as this represents the most important physiological repressor of AVP secretion.

Table 1 Criteria for definition of syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hyponatraemia*
Hypo-osmolality of plasma*
Continued renal excretion of sodium although taking no diuretics*
Absence of clinical evidence of fluid volume depletion*
Urinary osmolality greater than appropriate considering the plasma osmolality*
Normal renal function*
Normal adrenal function*
Normal thyroid function†

*Original definition of SIADH by Bartter & Schwartz, 1967 [3].
†Later amendment, described e.g. by Skowsky & Kikuchi, 1978 [7].

In the paper by Bartter & Schwartz 10 years later [3], the cardinal findings of SIADH were summarized as follows (Table 1): (i) hyponatraemia with corresponding hypo-osmolality of the serum and extracellular fluid; (ii) continued renal excretion of sodium; (iii) absence of clinical evidence of fluid volume depletion, i.e. normal skin turgor and blood pressure; (iv) osmolality of the urine greater than that appropriate for the concomitant tonicity of the plasma, i.e. urine less than maximally diluted; (v) normal renal function; and (vi) normal adrenal function. Later, another criteria was introduced: (vii) normal thyroid function [6, 7].

Usually, the plasma osmolality is < 280 mmol kg^{-1}, the urine osmolality is larger than the plasma osmolality and larger than 500 mmol kg^{-1} and the persistent urinary secretion of sodium exceeds 20 mEq L^{-1} in the absence of diuretic treatment. Not all reports and studies dealing with SIADH have strictly adhered to these criteria, but most have as minimum findings defining SIADH included hyponatraemia, serum hypo-osmolality, and a urinary hyper-osmolality characterized by continued sodium excretion.

The measurement of AVP in plasma is not a part

of the definition of SIADH, but the use of radioimmunoassay (RIA) determination of AVP makes it possible to define a 'RIA-SIADH' as inappropriately high plasma concentration of AVP at low plasma osmolality and simultaneous hypertonic urine [8, 9]. Such measurements are not yet mandatory for the diagnosis.

Pathophysiology

In 1963 Amatruda *et al.* [5] showed SIADH to be related to tumour production of antidiuretic hormone (ADH), also known as arginine-vasopressin (AVP). Normally, AVP is a product by the neurohypophyseal system with the cell bodies of the supraoptic and paraventricular nuclei synthesizing the octapeptides AVP and oxytocin in association with specific carrier proteins, the neurophysins [10, 11]. The function of the neurophysins is to act as binding proteins for AVP and oxytocin and there are different neurophysins for AVP and oxytocin [12]. Currently, there are no recognized special syndromes related to tumour production of neurophysins or oxytocin. The secretory granules migrate along the axons, through the median eminence, pituitary stalk, and into the posterior lobe of the pituitary gland, where they are stored in perivascular nerve endings. There they remain in storage until they are released by an action potential arising in the cell bodies. The hormones are freed from the carrier proteins at the time of secretion.

Arginine-vasopressin, oxytocin and neurophysins have been found by radioimmunoassay (RIA) in tumours [13–15], especially in tumours of small-cell lung cancer. Early data from Legros indicated that, whilst tumour related neurophysins seemed to be of the correct size and charge, these products did not become elevated in the plasma of patients with SIADH [14]. More recent studies by Legros *et al.* have now associated small-cell carcinoma of the lung both with production of some abnormal proteins and with high levels of plasma neurophysins [15]. A clear demonstration that cancer cells could synthesize AVP was first reported in 1969 from the *in-vitro* studies of Klein *et al.* [16] followed by those of George *et al.* in 1972 [17], showing the incorporation of radiolabelled cysteine into peptide identified as AVP. Subsequent studies have confirmed that AVP, oxytocin, and/or neurophysins are produced by the vast majority of small-cell lung cancers [18, 19].

Several reports indicate that neuropeptide production is not the exclusive property of small-cell lung cancers. In 1983, it was reported that a minor percentage of adenocarcinomas, squamous cell carcinomas, and large-cell carcinomas of the lung are also capable of the production and release of AVP [20]. Similar production of AVP has also been noted in prostatic and testicular cancers, ovarian cancer and pancreatic cancer [20]. More recently, immunocytochemical evidence for AVP production has been demonstrated sporadically in pituitary adenoma [21], olfactory neuroblastoma [22], breast cancer [23], colorectal cancer [23], and nasopharyngeal carcinoma [24, 25].

The normal physiological functions of AVP are confined to the kidney, the site of action being the distal and the collecting tubules of the nephron [26]. It increases the permeability of the segment of the nephron to water, and water reabsorption can then occur under the osmotic influence of the hypertonic renal medulla. Thus, AVP is an integral part of the homeostatic mechanism that controls water balance and effective blood volume [10]. The neurohypophyseal nuclei receive input from osmoreceptors that are believed to lie in or around the supraoptic nuclei, from volume receptors located in the left atrium and pulmonary veins, and from the renin–angiotensin system through the circulating levels of angiotensin II. The secretion of AVP is related to other mechanisms that are important for the maintenance of the constancy of the internal milieu, notably the first mechanism. An increase in plasma osmolality – through osmoreceptor stimulation, or a decrease in effective blood volume through volume receptor stimulation and through an increase in circulating angiotensin II levels – leads to a homeostatic increase in AVP secretion, and thus to renal water conservation. These stimuli also activate thirst, and thus cause increased water intake. These adjustments tend to restore plasma osmolality to normal and, in conjunction with other homeostatic mechanisms, help to restore effective blood volume [10]. The converse occurs in response to a decrease in plasma osmolality or an increase in blood volume. It is important to remember that the conservation of effective blood volume needs to supersede that of osmotic regulation. Thus, haemorrhage will trigger AVP release even in the presence of plasma hypoosmolality [10].

In addition, AVP secretion is also influenced by emotional factors and physical stress. These

Table 2 Differential diagnosis in syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Condition	References
Malignant tumours	[3]
Disorders involving the central nervous system	
Infections (meningitis, encephalitis, lues, abscess)	[3, 7]
Vasculitis (Lupus)	[7]
Hypoxic ischaemia insults	[7]
Head injuries (skull fracture, subdural contusion, subarachnoidal hemorrhage, thrombosis)	[4, 7]
Intracranial space occupying lesions (primary and metastatic tumors)	[4]
Guillain–Barré syndrome	[28]
Acute intermittent porphyria	[29]
Psychosis	[30]
Pain and emotional stress	[31]
Intrathoracic disorders	
Infections	
Tuberculosis	[32]
Bacterial pneumonia or empyema	[33]
Mycoplasma pneumonia	[34]
Viral	[35]
Fungal	[29]
Positive pressure ventilation	[36]
Decrease in left atrial pressure	[37]
Pneumothorax and atelectasis	[38]
Status asthmaticus	[39]
Cystic fibrosis	[40]
Mitral valve commisurotomy	[41]
Patent ductus arteriosus ligation	[42]
Atrial natriuretic peptide (ANP)	[43, 44, 45, 46, 47]
Drugs	[7]

influences probably operate via neural connections of the neurohypophyseal system with the limbic system, midbrain, and cerebral cortex [10].

The secretion of AVP is appropriate in terms of homeostatic needs if it occurs in response to plasma hyperosmolality or to hypovolaemia. When persistent secretion occurs in the absence of these stimuli, it leads to clinical manifestations grouped together under the label of syndrome of inappropriate antidiuretic hormone (SIADH). Possible causes of SIADH include an inappropriate excessive secretion of AVP from the hypothalamus or from extrahypothalamic tissues capable of such endocrine function.

Increased secretion of AVP from hypothalamus may be due to impairment of hypothalamic function caused by organic CNS disease, a variety of metabolic diseases (e.g. hypothyroidism and intermittent porphyrea) or stimulation of neurohypophyseal nuclei from false signals from volume receptors (e.g. caused by mitral commissurotomi) [10].

A variety of drugs may either enhance AVP secretion or enhance its effects on the distant nephron [27]. Such effects have been observed for narcotics, chlorpropamid, thiazides, carbomacepines, chlofibrat, vincristine, cyclophosphamide, and cisplatin [27].

An extrahypothalamic source of inappropriate AVP secretion has been observed in inflammatory states of non-endocrine tissues, particularly the lung [10]. Finally, AVP production may occur in a variety of malignant tumours as described below. The differential diagnoses in SIADH are given in Table 2 [3, 4, 7, 28–47]. Also, the effect of drugs in relation to SIADH will be reviewed in more detail below.

It has occasionally been described that SIAD may occur due to the production of an antidiuretic substance distinct from AVP [42]. Atrial natiuretic peptide (ANP), produced by human atrial tissue, has potent natriuretic activity. Several studies have demonstrated that it may be a circulating hormone producing hyponatraemia and SIAD [43–46]. Kamoi *et al.* [44] described a patient with SCLC and

Table 3 Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in primary brain tumours

Tumours	No. of patients with SIADH	Diagnostic criteria				Exclusions					References
		Hypo-natraemia	p-hypoosm.	u-hyperosm.	high u-Na	Drugs	Renal	Supra-renal	Thyroid	Hypo-volumia	
Astrocytomas											
Mesencephalic* astrocytoma	1	–	–	–	–	–	–	–	–	–	48
Optic glioma	1	+	+	+	+	–	+	+	+	–	49
Optic Chiasm glioma	1	+	+	+	–	–	–	–	+	–	50
Medulloblastom	1	+	+	+	–	–	–	–	–	–	51
Meningeoma											52
Choriod Plexus Papilloma	1	+	+	+	+	–	+	+	+	–	49
Neurofibroma	1	+	+	+	–	+	+	+	–	–	53
Neuroblastomas											
do.	1	+	+	+	+	+	+	–	–	–	54
do.	1	+	+	+	+	–	+	+	+	–	55
do.	1	+	+	+	+	+	+	–	+	–	56
Prolactinoma	1	+	+	+	–	–	+	+	+	–	57
Neurohypophyseal choriostoma	1	+	+	+	–	+	–	–	–	–	58

p-hypoosm., plasma hypoosmolality; u-hyperosm., urine hyperosmolality; high u-Na, high urine sodium; drugs, drug-related SIADH; renal, renal disease; suprarenal, suprarenal disease; thyroid, hypothyroidism; hypovol., hypovolumia.
*Criteria applied not stated.

hyponatraemia who had sustained high plasma levels of ANP, but normal levels of AVP, suggesting that ANP induced the hyponatraemia. In this case, evaluation of tumour tissue showed no ANP, indicating an increased secretion by atrial tissue. A subsequent study by Shimizu *et al.* [46] observed high levels of ANP together with AVP in tumour tissue from a patient with SCLC. A group of investigators [47] have evaluated cell lines from small-cell lung cancers (11 tumour cell lines from patients with SCLC and hyponatraemia and 10 cell lines from patients with SCLC and normal serum sodium values). Nine of the 11 tumour cell lines from hyponatraemic patients expressed ANP messenger RNA, whilst this was the case for eight out of 10 cell lines from patients with normal serum sodium values. Thus, ectopic production of ANP may be a co-factor together with ectopic production of AVP inducing SIADH, or ectopic production of ANP may alone induce a condition of SIAD.

Persistent secretion of AVP in conjunction with continued water intake will eventually lead to enhanced water conservation by the distant nephron, positive water balance in all body fluid compartments, and thereby cause an expanded blood volume and hypo-osmolality of the body fluid together with hyponatraemia. The urine which is excreted is hyperosmolar relative to the plasma hypo-osmolality. Because of the resulting expansion of blood volume, the glomerular filtration rate is increased and the renin–angiotensin–aldosterone mechanism is suppressed. These responses, together with renal haemodynamic adjustments lead to enhanced renal salt wastage. Such an adjustment will prevent further extracellular fluid volume expansion, and thus oedema will not occur. It will enable patients with SIADH to excrete a salt load promptly, and accordingly the urinary sodium will closely parallel the dietary sodium intake [9].

Tumours causing SIADH

SIADH has been reported to occur in a number of different primary brain tumours as outlined in Table 3. The syndrome has been observed in astrocytoma [48–50], medulloblastoma [51], meningeoma [52], choroid plexus papilloma [49], neurofibroma [53], neuroblastoma [54–56], prolactinoma [57] and neurohypophyseal choriostoma [58]. All observations have been in case reports including very few patients (Table 3). Thus, the frequency of SIADH in CNS tumours can therefore not be established.

Table 4 Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in haematologic malignancies

Tumours	No of. patients with SIADH	Diagnostic criteria				Exclusions					References
		Hypo-natraemia	p-hypoosm.	u-hyperosm.	high u-Na	Drugs	Renal	Supra-renal	Thyroid	Hypo-volumia	
Hodgkin's disease	1	+	+	+	+	−	+	+	+	+	59
Non-Hodgkin's disease	1	+	+	+	−	−	+	+	−	−	60
CLL	1	+	+	+	+	−	+	+	+	−	61
Multiple myeloma	1	+	+	+	+	+	+	+	−	−	62
Malignant histiocytosis	1	+	+	+	−	+	+	+	+	+	63

CLL, chronic lymphatic leukaemia.
For other abbreviations, see previous tables.

Table 5 Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in head and neck cancer and in intrathoracic non-pulmonary cancers

Tumours	No. of patients with SIADH/ Total no.	Diagnostic criteria				Exclusions					References
		Hypo-natraemia	p-hypoosm.	u-hyperosm.	High u-Na	Drugs	Renal	Supra-renal	Thyroid	Hypo-volumia	
Head- and neck cancer											
Squamous carcinoma of the tongue	1	+	+	+	+	+	+	−	−	+	64
Carcinoma of nasopharynx	1	+	+	+	−	+	+	+	+	−	24
Larynx	2	+	+	+	−	−	−	−	−	−	65
Glottis, larynx, pyriform sinus	4/260 (2%)	+	+	+	+	−	+	+	+	−	66
Head and neck cancers	43/1436 (3%)	+	+	+	−	−	+	+	+	−	67
Intrathoracic cancer											
Pleural mesothelioma	1	+	+	+	+	+	+	+	+	+	68
Pleural mesothelioma	1	+	+	+	−	−	−	−	−	−	69
Malignant thymoma	1	+	+	+	+	−	+	−	−	−	70
Pulmonary carcinosarcoma	1	+	+	+	+	−	+	+	+	−	71
Pleura, small cell carcinoma	1	+	+	+	−	−	−	−	−	−	72
Pulmonary malignant angio-endotheliomatosis	1	+	+	+	−	−	+	−	−	−	73

For abbreviations, see previous tables.

The diagnostic criteria applied for diagnosis of SIADH together with the exclusion criteria in the different studies cited are shown in Table 3. It is clear that not all studies have used the same diagnostic criteria and similarly the exclusion criteria have not been accounted for in all cases. The same is the case in other tumour types (Table 4–8).

Haematological malignancies associated with SIADH include Hodgkin's disease [59], non-Hodgkin's lymphoma [60], chronic lymphatic leukaemic [61], multiple myeloma [62], and malignant histiocytosis [63] (though only described in rare case reports) (Table 4).

With respect to head and neck cancer, SIADH has been noted in a variety of localizations of the tumours (Table 5) [24, 64–73]. Amongst patients with cancer of the head and neck only few cases with SIADH are reported. Two studies have reported SIADH to be present in 2% [66] and 3% [67] amongst the total numbers of 260 patients and 1436 patients with head and neck cancers, respectively.

Although most cases of SIADH are reported in

Table 6 Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in skin cancer and in gastro-intestinal cancers

Tumours	No. of patients with SIADH	Diagnostic criteria				Exclusions					References
		Hypo-natraemia	p-hypoosm.	u-hyperosm.	High u-Na	Drugs	Renal	Supra-renal	Hypo-Thyroid	volumia	
Skin tumours											
Melanoma	1	+	+	+	−	−	−	−	+	−	74
Gastro-intestinal cancer											
Oesophagus oat cell	1	+	+	+	+	−	+	−	−	−	75
Oesophagus	1	+	+	+	−	−	−	−	−	−	76
Gastric carcinoma	1	+	+	+	+	−	+	+	+	−	77
Pancreatic carcinoma	1	+	+	+	−	+	+	+	+	−	78
Pancreatic carcinoma	1	+	+	+	+	−	+	+	−	+	79
Colon cancer	1	+	+	+	+	−	+	+	+	+	80

For abbreviations, see previous tables.

Table 7 Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in gynaecologic cancers, breast cancer, prostatic cancer, bladder cancer and sarcoma

Tumours	No. of patients with SIADH	Diagnostic criteria				Exclusions					References
		Hypo-natraemia	p-hypoosm.	u-hyperosm.	High u-Na	Drugs	Renal	Supra-renal	Hypo-Thyroid	volumia	
Gynaecologic cancer											
Cervix uteri (small cell)	1	+	+	+	+	−	+	+	+	−	81
Corpus uteri (adenocarcinoma)	1	+	+	+	+	+	+	+	+	−	82
Breast cancer											
Breast cancer	1	+	+	+	−	−	−	−	−	−	83
Breast cancer	1	+	+	+	−	+	+	−	−	−	84
Prostatic cancer											
Prostata	1	+	+	+	+	+	+	+	+	−	85
Prostata small cell	1	+	+	+	+	−	+	+	+	−	86
Prostata	1	+	−	−	+	−	+	−	−	+	87
Bladder cancer	1	+	+	+	−	−	−	+	+	−	88
Sarcoma											
Ewings sarcoma	1	+	+	+	+	+	−	−	−	−	89
Reticulum cell sarcoma	1	+	+	+	−	−	+	−	−	−	90

For abbreviations, see previous tables.

lung cancer patients, also other intrathoracic malignancies may be associated with this syndrome, such as pleural mesothelioma [68, 69], malignant thymoma [70], and pulmonary carcinosarcoma [71]. Also malignant melanoma has been associated with SIADH [74].

Gastrointestinal cancers are rare causes of SIADH (Table 6) [74–80]. The syndrome has been reported in patients with oesophagus cancer, gastric carcinoma, pancreatic carcinoma and colon cancer (Table 6).

Rare cases of gynaecological cancers (cervix, uteri, and corpus uteri) have been associated with SIADH (Table 7) [81–90]. Also breast cancer and prostatic cancer may be associated with SIADH, but the frequency of the syndrome in this tumour type has not been determined.

The most frequent reports of SIADH have been observed in patients with lung cancers, and a number of studies have reported on the frequency (Table 8) [91–101]. Overall, a total of 214 cases of SIADH have been reported amongst 1473 patients with small-cell

Table 8 Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in lung cancer

Tumours	No. of patients with SIADH/ total no.	Diagnostic criteria				Exclusions					References
		Hypo-natraemia	p-hypoosm.	u-hyperosm.	High u-Na	Drugs	Renal	Supra-renal	Thyroid	Hypo-volumia	
Small-cell lung cancer (SCLC)											
SCLC	25/69 (36%)	+	+	+	−	+	+	−	−	−	91
SCLC	8/84 (10%)	−	−	−	−	−	−	−	−	−	92
SCLC	40/106 (38%)	+	+	+	−	−	+	+	+	−	93
SCLC	16/98 (16%)	+	−	+	−	−	+	+	−	−	94
SCLC	23/103 (22%)	+	+	+	+	−	+	+	+	+	95
SCLC	18/250 (7%)	+	+	+	+	−	+	+	−	+	96
SCLC	8/106 (8%)	+	+	+	−	−	+	+	+	+	97
SCLC	32/226 (14%)	+	+	+	−	−	−	−	−	−	98
SCLC	40/350 (11%)	+	+	+	+	+	+	+	+	−	99
SCLC	2/39 (5%)	+	+	+	−	−	+	+	−	−	100
SCLC	2/42 (5%)	+	+	+	−	−	−	−	−	−	101
Total	214/1473 (15%)										
Non-small-cell lung cancer (NSCLC)											
NSCLC	1/56 (2%)	+	+	+	+	−	+	+	+	+	95
NSCLC	1/147 (0.7%)	−	+	+	−	−	−	−	−	−	100
NSCLC	1/224 (0.4%)	+	+	+	−	−	−	−	−	−	101
Total, NSCLC	3/427 (0.7%)										

For abbreviations, see previous tables.

lung cancer (15%), indicating that small-cell lung cancer is the most frequent malignant disease associated with this syndrome. As with the previous Tables, all studies have not applied entirely similar diagnostic criteria or accounted for all exclusion criteria.

SIADH in patients with non-small-cell lung cancer are much less frequent. In three series, a total of three patients with the syndrome were noted amongst 427 patients with non-small-cell lung cancer (0.7%) (Table 8).

SIADH caused by drugs

A growing number of pharmaceutical agents have been shown to produce SIADH (Table 9) [102–128]. The mechanisms by which these drugs lead to water intoxication has only partly been elucidated. It should be noted that no drug can produce the syndrome without adequate (or excessive) oral intake. Thus, the essential condition for SIADH ('osmolality of intake' lower than 'osmolality of output') applies to drug-induced SIADH precisely as it applies to other forms of SIADH.

The principle mechanisms leading to SIADH are augmented renal action of AVP (e.g. by sulfonylureas), impaired renal water excretion independent of AVP (e.g. by clofibrate, carbamazepine, vincristine, vinblastine, cyclophosphamide, or morphine) and non-osmolar stimulation of AVP release mediated by baroreceptors (e.g. by thiazide diuretics or nicotine) [129].

Clinical presentation

Water intoxication with hypo-osmolality of plasma and hyponatraemia may cause neurological dysfunctions. In mild cases, patients may complain of fatigue, anorexia, nausea, diarrhoea and headaches [130]. When the serum sodium falls below 115 mEq L^{-1}, altered mental status, confusion, lethargy, psychosis, seizures, coma and occasionally death may occur. Additional signs of profound hyponatraemia include pathological reflexes, papil oedema, and, rarely, focal neurological signs [131].

However, cancer patients may develop hyponatraemia for similar reasons as patients without cancer. These aetiologies include severe liver disease, cardiac failure, renal disease, hypothyroidism, excessive gastrointestinal fluid and electrolyte losses, and glucocorticoid deficiency (Table 2). Iatrogenic causes, such as medical therapy should also be

Table 9 Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) caused by drugs

Drugs	References
Cytotoxic chemotherapy	
Vincristine	102, 103
Vinblastine	104, 105, 106
Cisplatin	107, 108, 109, 110, 111
Cyclophosphamide	112
Melphalan	113
Levamisole	114
Endocrine treatment	
Aminoglutethimide	115
Sulfonylurea	116, 117
Clofibrate	118
Thiazide diuretics	119, 120, 121
Carbamazepine	4
Tricyclic antidepressants	122, 123, 124, 125
Nicotine	126, 127
Morphine	126, 128

considered in evaluating patients with hyponatraemia (Table 9). Volume depletion with resulting dilutional hyponatraemia should be excluded by physical examination.

Therefore, when evaluating patients with hyponatraemia, a careful history and physical examination should be performed together with adequate paraclinical measures in order to assess the criteria for definition of SIADH as outlined in Table 1. Other causes of dilutional hyponatraemia should also be excluded as outlined in Table 2 in order to be able to choose the rational therapy for the condition in the particular patient.

The occurrence of SIADH [131], or serum values of AVP [132] have been used as tumour markers in small-cell lung cancer patients. Biochemical abnormalities are reduced after tumour regression, but a completely normal renal water handling are achieved in only a few patients, even when complete clinical remission of the tumour is achieved [131]. The serum ADH level has not been useful in defining the tumour burden or the presence of malignant disease in individual patients [132]. The presence of SIADH in patients with small-cell lung cancer has been associated with a detrimental effect on survival in one study [92], whilst it was of no prognostic significance for survival in another study including 106 patients [94]. Similarly, a study by List *et al.* studied 350 patients with small-cell lung cancer, including 40 patients with SIADH, and reported that the presence of SIADH did not influence either response to chemotherapy or overall survival [99].

Treatment of SIADH

The most effective treatment for SIADH is successful eradication of the underlying tumour. In small-cell lung cancer, the tumour usually responds to initial combination chemotherapy with subsequent resolution of any associated SIADH. Thus, chemotherapy was shown to correct the hyponatraemia in 17 or 18 small-cell lung cancer patients [133]. However, the therapy for SIADH both in previously untreated and in refractory cancer often involves other measures which are usually effective, both when used alone or when in combination with specific antineoplastic treatment of the tumour. If SIADH is due to brain metastases or primary brain tumours, radiotherapy and corticosteroid therapy may be effective [134]. For patients with symptomatic hyponatraemia and serum sodium less than 130 mEq L^{-1}, fluid restriction to less than 500 mL day^{-1} slowly but effectively causes an increased serum sodium in the majority of patients [134]. Fluid restriction can be compatible with chemotherapy that requires hydration (e.g. to prevent haemorrhagic cystitis with high-dose cyclophosphamide, or in cisplatin-based chemotherapy) provided that the patient is carefully monitored and given normal saline with diuretics and electrolyte replacement.

Patients with life-threatening hyponatraemia with coma or convulsions may be treated by infusion of 3% hypertonic saline together with intravenous furosemide. The rate of rise in serum sodium should be limited to 0.5–1.0 mEq L^{-1} h^{-1} to minimize the risk of central pontine myelinolysis. The saline is given to raise sodium levels and the furosemide to speed the process by inducing negative fluid balance. This treatment requires careful monitoring of urinary sodium and potassium losses, with intravenous replacement of the appropriate amount of sodium chloride and potassium chloride [135].

Patients in whom the SIADH is unresponsive to fluid restriction, or who are unable to comply with a need for therapeutic intervention in addition to the specific antineoplastic treatment, may be treated with drugs that specifically inhibit the secretion or the renal effect of AVP. Three drugs have such effects: diphenylhydantoin, dichlormethyl tetracycline (demeclocycline) and lithium, of which demeclocycline is the most widely applied. Diphenylhydantoin can block the release of AVP from the neurohypophysis [136], but it has the disadvantage

of intravenous administration. Both demeclocycline and lithium act by directly blocking the renal tubular effect of AVP by inhibiting AVP-induced cAMP formation and blocking the effect of any cAMP generated [137, 138]. They are indicated in patients in whom the syndrome is not self-limited and in whom the underlying cause cannot be removed. In such cases, an oral drug taken for a prolonged period would be the most desirable. Whilst both drugs have toxic effects, the antibiotic demeclocycline appears to be the best tolerated, with more reproducibility of effect, and is hence the most widely applied. Demeclocycline causes a nephrogenic diabetes insipidus that is reversible and dose-dependent [130, 139], and reliably raises the serum sodium in patients with SIADH. In a series of cancer patients with SIADH, all 15 patients receiving demeclocycline responded with increased serum sodium to $\geqslant 130\ \text{mEq L}^{-1}$ in an average of 3 days [130]. The correction of serum sodium with demeclocycline does not require fluid restriction. Azothemia is the only toxicity associated with demeclocycline therapy, and it can be severe in some patients. The recommended initial dose of demeclocycline is $600\ \text{mg day}^{-1}$, as greater renal toxicity is seen when $1200\ \text{mg day}^{-1}$ is administered [130]. The total dose is divided and given two or three times daily.

In conclusion, SIADH is a relatively frequent finding in patients with small-cell lung cancer, and it has also been reported to occur in a large number of other malignancies, although only sporadically. In order to ensure proper treatment, the criteria for diagnosis of SIADH should be applied and the numerous differential diagnoses accounted for. As expected, the optimal therapy for SIADH is to treat the underlying malignant disease. If this is not possible or if the disease becomes refractory, other treatment measures are available such as water restriction, demeclocycline therapy or, in severe cases, infusion of hypertonic saline together with furosemide during careful monitoring.

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