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BRIEF REPORT

Characteristics and Mortality of *Pneumocystis* Pneumonia in Patients With Cushing's Syndrome: A Plea for Timely Initiation of Chemoprophylaxis

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In patients with Cushing's syndrome, development of *Pneumocystis* pneumonia (PCP) is associated with extreme cortisol production levels. In this setting, immune reconstitution after abrogation of cortisol excess appears to induce development of symptomatic PCP. The high mortality rate warrants timely initiation of chemoprophylaxis or even preemptive treatment of PCP.

Keywords. Cushing's syndrome; immune reconstitution; PCP; *Pneumocystis jirovecii*; prophylaxis.

Implementation of prophylaxis guidelines reduced the incidence of *Pneumocystis* pneumonia (PCP) in human immunodeficiency virus (HIV)-infected and transplant recipient populations over the past decades [1, 2]. However, there is an increasing number of patients who develop PCP due to other causes of acquired immunodeficiency [3]. Because of deprivation of leukocyte, T-cell, and macrophage function by prolonged exposure to supra-physiological levels of cortisol, patients with Cushing's syndrome are at risk of acquiring PCP. The endogenous cortisol excess responsible for the clinical phenotype of Cushing's syndrome can be either caused by an adrenocorticotropic hormone (ACTH)-producing pituitary adenoma, adrenal adenoma or hyperplasia, or ectopic (sometimes malignant) sources of ACTH or corticotropin-releasing hormone (CRH) production [4].

The clinical presentation and course of PCP in patients with Cushing's syndrome may differ from patients with PCP due to other underlying conditions [5, 6]. Treatment for Cushing's syndrome involves surgical treatment, ie, (1) removal of the pituitary or adrenal adenoma or ectopic tumor and/or (2) blockage of cortisol production by metyrapone or ketaconazole [7]. Thereafter, the functional recovery of immune cells commences [8, 9]. This may subsequently lead to a potent inflammatory reaction to *Pneumocystis jirovecii* in the lungs, resulting in a clinical presentation of PCP as an immune reconstitution inflammatory syndrome [10]. Because of the very low annual incidence of Cushing's syndrome (approximately 0.2–5.0 per million individuals), reliable estimates of the incidence of PCP in this population as well as risk-enhancing characteristics and PCP-attributable mortality rates are unknown. We report the observations on 5 patients with PCP in a cohort of 53 patients with Cushing's syndrome, and our institution serves as a national referral center for this disease. The issue of appropriate chemoprophylaxis in this patient population is concisely discussed in conjunction with a systematic review of the literature.

METHODS

All patients diagnosed with Cushing's syndrome and treated between January 1, 2003 and July 1, 2015 were included. Data about the cause of Cushing's syndrome, levels of morning serum cortisol, ACTH serum levels, midnight salivary cortisol, 24-hour urinary free cortisol excretion (24-h UFC), and outcome were obtained from the electronic patient records. *Pneumocystis* pneumonia was regarded as confirmed if clinical and radiological findings were suggestive for PCP and a bronchoalveolar lavage fluid provided microbiological evidence of the presence of *P jirovecii* (by polymerase chain reaction and/or Giemsa and silver staining). Univariate non-parametric tests were performed for comparison of patient characteristics and laboratory results between patients with and without PCP. Standard PCP chemoprophylaxis was not prescribed. A waiver for informed consent and permission for conduct of the study was obtained from the institutional review board.

A systematic review of PCP in patients with Cushing's syndrome was conducted using Medline databases (search strategy: see Supplement 2). All articles describing patients with Cushing's syndrome and PCP, for whom at least 1 cortisol measurement was reported, were included. Articles were independently assessed by 2 of the investigators (K. v. H. and L. V.). Of the selected articles, the literature references were reviewed to identify potential articles missed by the initial search strategy.

RESULTS

Between January 2003 and July 2015, 53 patients were diagnosed with Cushing's syndrome and they were included in the study. The median age was 49 years (range, 15–74 years), and 39

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(73.6%) patients were female. Common causes of Cushing's syndrome, ie, pituitary micro- and macroadenoma, adrenal gland adenoma, or hyperplasia, were present in 46 (87%) patients, and 7 patients had a malignant and/or ectopic cause of hypercortisolism. Five patients developed PCP after initiation of cortisol-lowering therapy. The characteristics of these patients are described in Table 1. In 4 of these patients, Cushing's syndrome was caused by an ectopic source of ACTH or CRH production. Higher levels of morning serum cortisol, midnight salivary cortisol, and 24-h UFC were associated with increased risk for development of PCP ($P = .02$, $P = .05$, and $P = .003$, respectively; Mann-Whitney U test). Of patients with Cushing's syndrome, 4 of 53 patients (7.5%) had a 24-h UFC above 10 000 nmol (>67 times upper limit of normal [ULN]), all of whom developed PCP (see Supplement 1, Figure 1).

The systematic review identified 25 publications, 11 of which were excluded because cortisol values were not reported (10 patients) and/or lack of a confirmed PCP diagnosis (3 patients). The 14 included articles reported a total of only 15 patients with Cushing's syndrome and PCP (Table 1). In 13 of 15 patients, development of PCP was reported to occur after initiation of cortisol blocking therapy. All but 1 patient had ectopic Cushing's syndrome. Twenty-four-hour UFCs were only available in 8 cases, and, of these, 5 patients had levels above 10 000 nmol/24 hours. The case fatality rate was high: 11 of 15 patients died. If reported, the most common cause of death was respiratory insufficiency.

DISCUSSION

A limited number of previous reports indicated that the risk for a spectrum of opportunistic infectious diseases in patients with Cushing's syndrome is related to the level of excess cortisol production [10, 11]. In accordance with this biologically plausible observation, we found a strong association between

Table 1. Patients With *Pneumocystis* Pneumonia and Cushing's Syndrome

Author (Ref. No.)[a]	Age	Sex	Cause of Cushing's Syndrome	Serum Cortisol (nmol/L)	Urine Cortisol (nmol/24 h)	Onset PCP Before or After Start of Treatment	Microbiology Specimen (Method)	Outcome
Chowdry [15]	48	F	ACTH producing NET	2930	45 082	After	Autopsy	Death$^{(R)}$
Gabalec [16]	60	F	Occult ectopic ACTH secretion (unknown origin)	3150	13 630	After	BALF	Alive
Gabalec [16]	20	M	ACTH producing high-grade endocrine carcinoma	>1380	1188	After	BALF	Alive
Chang [17]	60	M	Occult ectopic ACTH secretion (unknown origin)	4365	NA	Before	Blood (PCR)	Death$^{(R)}$
Arlt [18]	36	M	ACTH producing metastatic NET of the right kidney	2180	9180	After	BALF (IF)	Death$^{(R)}$
Oosterhuis [8]	57	F	ACTH producing NET pancreas	2371	294 306	After	BALF	Death
Keenan [9]	26	F	Occult ectopic ACTH secretion (unknown origin)	1291	31 000	After	BALF	Alive
Kim [19]	60	F	Occult ectopic ACTH secretion (unknown origin)	2207	NA	After	BALF (Giemsa stain)	Death$^{(R)}$
Bakker [20]	56	M	Occult ectopic ACTH secretion (unknown origin)	5450	51 460	After	BALF	Death$^{(R)}$
Collichio [21]	53	M	SCLC	>1380	NA	After[b]	BALF (cytology)	Death
Russi [22]	23	M	Pituitary microadenoma	2759	NA	After	BALF (IF)	Alive
Dimopoulos [23]	49	F	SCLC	1766	NA	After	Autopsy	Death$^{(R)}$
Sieber [24]	66	M	Ectopic CRH producing oat cell carcinoma of the lung	3200	NA	Before	Biopsy	Death
Fulkerson [25]	38	F	ACTH producing thymus carcinoma	NA	10 × ULN[c]	After	Autopsy (silver stain)	Death
Natale [26]	24	M	ACTH producing carcinoid	3035	130 × ULN[c]	After	BALF (silver stain)	Death
This report	70	F	Thymic carcinoid	8800	52 934	After	BALF (Giemsa + silver stain)	Death$^{(R)}$
This report	29	F	Adrenal adenoma	500	57 564	After	BALF (PCR)	Alive
This report	74	M	ACTH producing pheochromocytoma	1330	10 238	After	BALF (PCR)	Alive
This report	61	F	SCLC	1600	16 090	After	BALF (PCR)	Death$^{(R)}$
This report	36	F	Adrenal carcinoma	870	790	After	BALF (PCR)	Death$^{(R)}$

Abbreviations: ACTH, adrenocorticotropic hormone; BALF, bronchoalveolar lavage fluid; IF, immune fluorescence; NA, not available; NET, neuroendocrine tumor; PCP, *Pneumocystis* pneumonia; PCR, polymerase chain reaction; *(R)*, as superscript to outcome indicates respiratory failure was reported to cause—or at least contributed to—an adverse outcome; SCLC, small cell lung carcinoma; ULN, upper limit of normal.

[a]References of the included articles of the systematic review of the literature.

[b]Therapy for SCLC was started before PCP symptoms, no direct cortisol-lowering therapy.

[c]No exact value available.

the development of PCP and the degree of exposure to cortisol excess (as reflected by 24-h UFC, serum, and midnight salivary cortisol levels). In addition, PCP was diagnosed in 1 of 46 (2%) patients who had a pituitary or adrenal adenoma versus 4 of 7 (57%) patients with ectopic Cushing's syndrome. The former patient developed Cushing's syndrome during pregnancy due to an adrenal adenoma, and the cortisol excess as reflected by 24-h UFC exceeded 50 000 nmol. Within our study population, ectopic or malignant neoplasms more frequently caused extreme levels of hypercortisolism. In concurrence, but possibly influenced by publication bias, the literature review showed that malignant and ectopic Cushing's syndrome patients were overrepresented as patients also diagnosed with PCP. The occult nature of these conditions may delay correct diagnosis and treatment. This further enhances the cumulative exposure to steroid hormones, which probably best defines the individual's risk for development of PCP [12].

The high mortality rate of 60%–65% (study cohort and literature review, respectively) is of major concern. This exceeds reported PCP mortality rates of 10%–40% in populations with other underlying conditions, eg, HIV and solid organ transplantation [13]. Several factors may account for this observation. First, the very low incidence of Cushing's syndrome may cause physicians to be unfamiliar with related infectious complications, delaying diagnosis and treatment of PCP. Second, a range of other fatal events is prone to occur in patients with severe Cushing's syndrome. Furthermore, the treatment with high-dose steroids in severe cases of PCP may not have the maximum reducing effect on mortality because of the already maximal decreased sensitivity of immune cells for steroid compounds [14].

It is notable that, in the majority of patients, PCP was diagnosed after initiation of cortisol-lowering therapy. The systematic review confirmed that PCP often becomes manifest after initiation of treatment for hypercortisolism. This strongly suggests that immune reconstitution is an important component or even a prerequisite for development of clinically overt PCP in this population. During prolonged hypercortisolism, patients may acquire an ever-accumulating lung burden of *P jirovecii*, whilst the high level of cortisol suppresses the inflammatory response. A vigorous inflammatory reaction can develop only after an abrupt decrease of cortisol levels. Both—but in particular the combination of—a relatively high fungal burden and a sudden reversal of immune repression can be expected to negatively impact the outcome of PCP.

At present, the management of Cushing's syndrome does not routinely include PCP prophylaxis or preemptive treatment [7, 9, 10]. Similar to all antimicrobial chemoprophylaxis, the indication of PCP prophylaxis in patients with Cushing's syndrome depends on a harm-benefit analysis. Although larger cohorts would provide more reliable estimates, the number of patients needed to be treated with chemoprophylaxis to prevent 1 PCP case is probably <50. From the available but limited data, it can be deduced that the presence of ectopic or malignant causes of Cushing's syndrome as well as extreme levels of cortisol (ie, in the 5th percentile, ie, >20 times the ULN) point towards a very high risk for development of PCP. Taking mortality rates into account, the benefits strongly weigh against the limited toxicity and side effects usually caused by a prophylactic dosage of trimethoprim-sulfamethoxazole (TMP-SMX). The duration of prophylaxis should be extended to the time that the effects of hypercortisolism on the immune system have waned.

CONCLUSIONS

Due to the very low incidence of Cushing's syndrome, an adequate PCP chemoprophylaxis strategy should now be constructed based on the available observational data. Based on previous studies and on our own experience, we recommend PCP chemoprophylaxis for all patients diagnosed with Cushing's syndrome, especially those with high 24-h UFCs. As a consequence of the potential role of immune reconstitution, a patient with Cushing's syndrome should preferably start PCP chemoprophylaxis before initiation of cortisol-lowering therapy. Of note, any delay in optimal management of the Cushing's syndrome should be avoided. In addition, with regard to the very high mortality rate of PCP in patients with Cushing's syndrome, either preemptive therapy of PCP with high-dose TMP-SMX or chemoprophylaxis plus assertive monitoring is indicated for patients with an increased risk profile (ectopic Cushing's syndrome or extreme cortisol levels).

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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