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EDITORIAL

Stroke and sleep-disordered breathing: A relationship under construction

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Abstract

The association between sleep-disordered breathing (SDB) and cardiovascular risk has been the focus of attention in recent years. Sleep disorders are emerging risk factors for cardiovascular disease and have been related to the whole spectrum of stroke, including transient ischemic attack, ischemic cerebral infarction and intracerebral haemorrhage. It has been shown that lacunar stroke or lacunar infarctions affecting the internal capsule or the protuberance are associated with a higher frequency of SDB. Acute stroke patients with associated SDB have a worse prognosis and a higher mortality as compared to patients with first-ever stroke without SDB. Preliminary studies provide evidence of the usefulness of treatment with continuous positive airway pressure when SDB is present in stroke patients.

Key words: Apnea-hypopnea index; Cardiovascular risk factors; Continuous positive airway pressure; Ischemic stroke; Lacunar infarction; Sleep disordered

Core tip: Sleep disorders including obstructive sleep apnea are associated with an increased risk for a number of cardiovascular diseases, notably acute cerebrovascular events. A number of studies have shown a high prevalence of sleep-related breathing disorders in patients with stroke. A decrease in cerebral perfusion and increased coagulability related to metabolic, hematological and hemodynamic changes occuring in the presence of sleep-related breathing disorders are proposed as potential mechanisms in the pathogenesis of stroke. Early diagnosis and prompt therapeutic measures, including continuous positive airway pressure are necessary to reduce the stroke risk associated with sleep disorders. Sleep-related breating disorders should be considered modifiable risk factors for stroke, although they are frequenty underdiagnosed. The relationship between sleep breathing disorders and stroke should be further investigated for improving primary and secondary stroke prevention strategies and to contribute to reduce the global burden of stroke.

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INTRODUCTION

Sleep-disordered breathing (SDB) and stroke, a relationship story that from our point of view is a sort of story not yet ended, since as we shall see, is still under construction.

One of the first reports from the Sleep Heart Health Study[1] postulated an association of SDB with cardiovascular disease. A total of 6424 subjects were included in a cross-sectional study and underwent fully polysomnography at home. Sixteen percent reported at least one manifestation of cardiovascular disease, such as heart failure, angina, myocardial infarction, stroke or revascularization procedure. Considering upper *vs* lower apnea-hypopnea index (AHI) quartile, SDB was associated more strongly with heart failure (OR = 2.38, 95%CI: 1.22-4.62) and stroke (OR = 1.58, 95%CI: 1.02-2.46) than with coronary heart disease (OR = 1.27, 95%CI: 0.99-1.62). Therefore, this study shows that the effects of SDB were compatible with heterogeneous manifestations of cardiovascular disease, including stroke. Later on, other studies, among which the publication of Marin *et al*[2] has been probably one of the most cited, showed that the presence of SDB was related with an increase in cardiovascular morbidity and mortality especially when obstructive apnea was not treated with nasal continuous positive airway pressure (CPAP). Moreover, in a systematic review of the interaction of cardiovascular pathophysiology and obstructive sleep apnea, several of the mechanisms identified (sleep fragmentation, increased oxidative stress, metabolic dysregulation, increased sympathetic activation, increased platelet aggregability and vascular endothelial dysfunction) were described as possible explanations for implicating obstructive sleep apnea in the pathogenesis of hypertension and also as a contributing factor to stroke and cerebrovascular disease[3]. Much research has been done dealing with the association of SDB with hypertension and cardiac diseases, but there are fewer data regarding the relationship with stroke.

We here present an overview of salient findings regarding different aspects of the relationship between SDB and stroke, including SDB frequency, SDB types and clinical presentation, SDB as a risk factor for stroke and SDB as a prognostic factor for stroke, as well as treatment options in patients with SDB. Data here presented is based on a selective review of the literature of the most relevant publications that according to the author's criteria are of the interest of the readers. This information is presented together with data related to the experience of our group in the management of stroke patients with SDB.

A meta-analysis of the frequency of sleep apnea in patients with stroke and transient ischemic attack (TIA), which included 29 studies with 2343 patients, found that SDB was present in 71.4% of patients for AHI > 5 and in 14% for AHI > 40[4]. Also, the percentage of patients with AHI > 10 was higher among patients with recurrent stroke as compared to patients with first-ever stroke (73% *vs* 57%, P = 0.013) as well as in males than females (65% *vs* 48%, P = 0.001). Interestingly, patients with stroke of unknown cause (undetermined stroke) showed the highest incidence of SDB, confirming that SDB influences cerebrovascular events beyond its association with traditional cardiovascular risk factors. The findings of this meta-analysis support the need for screening for SDB in all TIA and stroke patients[4].

In a prospective study of 161 patients admitted to our stroke unit undergoing a portable respiratory recording study within 48-72 h after admission, AHI > 10 was recorded in 71.4% of cases and AHI > 30 in 28% (Table 1)[5]. In relation to the type of events and their clinical presentation, any types of respiratory events were observed, including obstructive, mixed and central apneas as well as Cheyne-Stokes (CS) breathing pattern. CS respiration was present in 26% of the patients. Differences in the percentage of patients with AHI > 10 and AHI > 30, which can be considered a severe sleep apnea, in relation to the different stroke subtypes (TIA, ischemic and hemorrhagic stroke) were not found. On the other hand, patients were neither obese nor had daytime somnolence according to results of the Epworth Sleepiness Scale. Three months after the acute phase of stroke, there was a reduction of SDB, mainly due to a decrease in central respiratory events. These results, in some way, led us to hypothesize that most obstructive apnea events were previous to stroke (perhaps acting as a risk factor) and that central obstructive events and CS respiration were secondary to stroke[5].

In this previous study, a correlation between the presence of SDB and the topography of stroke could not be established given that lesions were often too large and involved different cerebral areas. For this reason, we examined the occurrence of SDB in patients with lacunar stroke. Lacunar stroke is characterized by small, localized brain ischemic lesions with a maximum diameter smaller than 20 mm found in the blood supply of a penetrating arteriole, affecting different subcortical topographies[6,7]. In a clinical series of 68 patients with proven lacunar infarction, SDB was frequent, with 69% of patients showing AHI $\geqslant$ 10, 44% AHI $\geqslant$ 20, and 25% AHI $\geqslant$ 30. Variables independently associated with SDB were determined by logistic regression analysis. As shown in Table 2, smoking and topography of lacunes in the pons or the internal capsule were significant predictors of SDB. Body mass index was inversely associated with SDB. Therefore, smoker patients with capsular or pontine lacunar infarction should be screened for SDB[8]. Surprisingly, CS respiration was documented

Table 1 Sleep-related parameters in 161 consecutive patients with first-ever stroke included in the "Sagrat Cor Hospital of Barcelona Stroke Registry"[5]

Data	Transient ischemic attack (n = 39)	Ischemic stroke (n = 112)	Hemorrhagic stroke (n = 10)	Total (n = 161)
Age, yr, mean (SD)	67.9 (10.1)	72.5 (8.9)	73 (10.5)	72 (9)
Body mass index, kg/m^2, mean (SD)	27.3 (4.6)	26.2 (3.7)	26.7 (2.6)	26.6 (3.9)
Epworth sleepiness scale, score, mean (SD)	47 (3.3)	4.9 (3.3)	4.3 (2.1)	4.8 (3.3)
AHI, mean (SD)	19.4 (16.7)	21.5 (15.7)	25 (11.9)	21.2 (15.7)
OAI, mean (SD)	5.9 (10.2)	3.9 (7.8)	5.4 (6.7)	4.5 (8.4)
CAI, mean (SD)	3.32 (7.9)[a]	5.9 (10.1)	11.1 (15.1)[a]	5.6 (10.1)
Cheyne-Stokes breathing pattern, n (%)	8 (20.5)	31 (27.7)	3 (30)	42 (26.1)
AHI, n (%)				
> 10	24 (61.5)	83 (74.1)	9 (90)	116 (72)
> 30	10 (25.6)	31 (27.7)	4 (40)	45 (27.9)
CT90%, mean (SD)	8.2 (13.1)	8.1 (17.8)	5.7 (7.1)	7.8 (15.7)

CAI: Central apnea index; AHI: Apnea-hypopnea index; OAI: Obstructive apnea index; CT90%: Percentage of time below 90% arterial oxygen saturation; TIA: Transient ischemic attack. [a]P = 0.03 between CAI of TIA patients and CAI of patients with hemorrhagic stroke.

Table 2 Variables independently associated with different sleep-disordered breathing in a clinical series of 68 patients with first-ever lacunar infarction[8]

Model	β	SE (β)	OR (95%CI)	P value
AHI ⩾ 10				
Topography in the internal capsule or pons or smoking	1.153	0.576	3.17 (1.02-9.79)	0.045
AHI ⩾ 20				
Smoking and topography in the internal capsule or pons	2.225	1.111	9.25 (1.05-81.70)	0.045
AHI ⩾ 30				
Smoking	2.977	1.255	19.64 (1.68-229.85)	0.018
Body mass index	0.520	0.203	1.68 (1.13-2.50)	0.010

AHI: Apnea-hypopnea index; SE: Standard error.

in 20.6% of patients, which was in contrast with the previous idea that CS breathing pattern usually occurs in large strokes with unfavourable prognosis. Patients with CS respiration as compared with those without CS respiration showed higher AHI and central apnea index as well as higher scores of the Barthel index and the Canadian Neurological scale as a measure of stroke severity, and longer hospital stay[9].

But which are the evidences that we have about SDB being a risk factor for stroke? Two large cross-sectional studies, the Sleep Heart Health Study[1] and the Wisconsin Sleep Cohort Study[10] found an association between SDB and stroke, after adjusting for confounders and also a dose-response effect. Furthermore, longitudinal data of the Wisconsin Sleep Cohort showed a higher occurrence of stroke during a 4-year follow-up period in patients with high AHI, although statistical significance was not reached probably due to the low statistical power related to the sample size[10]. Further data from the Sleep Heart Health Study, with 5422 participants without a history of stroke at the baseline examination and untreated for sleep apnea followed for a median of 8.7 years, revealed that the adjusted hazard ratio increased with each one unit increase in obstructive AHI (OAHI). Patients with an AHI > 20 had a worse survival. In men, each one unit increase in OAHI was estimated to increase stroke risk by 6%[11]. In a meta-analysis of 17 prospective cohort studies to assess the effect of obstructive sleep apnea (OSA) on cardiovascular events, it was concluded that moderate to severe OSA increased significantly the risk of cardiovascular diseases, particularly stroke risk[12].

And what about SDB as a prognostic factor for stroke? In 1996, Good *et al*[13] already shown that arterial oxyhemoglobin desaturation (SaO_2) correlated with lower functional abilities as measured by the Barthel index at discharge and at 3 and 12 mo of follow-up. The study of Kaneko *et al*[14] in 2003, showed that patients with sleep apnea and stroke had lower functional capacity as compared to patients without sleep apnea, and also had longer periods of hospitalization and rehabilitation.

In our chort of 161 patients with TIA or a first-ever stroke followed over 2 years, AHI > 30 was an independent factor of poorer survival (Figure 1), with an implied 5% increase in mortality risk for each additional AHI unit[15]. Results of this study indicate that SDB may be considered an independent prognostic factor related to fatal outcome after a first stroke episode[15]. Similar results were obtained in other studies, in which the presence of OSA in stroke patients was associated with an increased risk of early death as compared to patients without OSA[16,17].

Most of the pathophysiological mechanisms described as being involved in the development of cardiovascular disease as a whole, could also be applied to stroke in

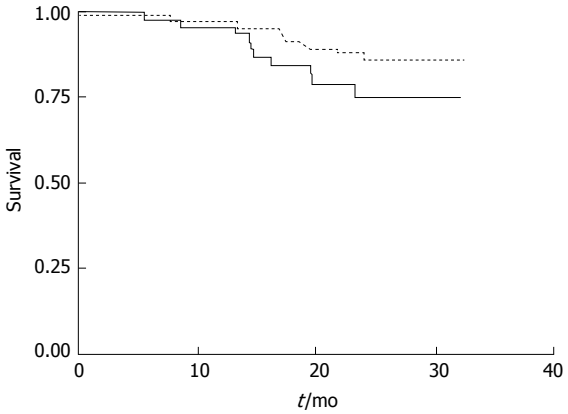

Figure 1 Kaplan-Meier survival estimates in patients with an apnea-hypopnea index < 30 (dash line) and in those with apnea-hypopnea index ⩾ 30 (solid line). Greater mortality in patients with an AHI above the cut-off value of 30. AHI: Apnea-hypopnea index.

particular. However, some more specific mechanisms have been identified in the cerebral circulation of patients with OSA. It has been shown that SDB could induce damage in the penumbra area (the area surrounding an ischemic event, which is at risk of progressing to infarction, but is still salvageable if re-perfused). Different mechanisms such as a decrease and variation in cerebral blood flow has been demonstrated using transcranial Doppler examination during apneas[18]. In this respect, Valipour *et al*[19] have observed decreases in cerebral oxygenation during apneas and hypopneas, which could also contribute to affect the penumbra area and impair prognosis.

The preceding paragraphs have shown that sleep disorders are more frequent in stroke, that they play a role as risk and prognostic factor in stroke patients, and that both disorders, SDB and stroke, are possibly linked by several underlying pathophysiological mechanisms. The next question to be answered is whether there is a rationale for treatment of SDB in stroke patients[20]. Nasal CPAP is an effective and safe method for OSA but its role in the management of SDB in stroke patients remains unclear. However, in relation to pathophysiological mechanisms, nasal CPAP has shown to be useful for decreasing platelet activation markers, soluble CD40 ligand (sCD40L) and soluble P-selectin (sP-selectin), in patients with moderate to severe OSA and silent brain infarction[21]. In another study, treatment with CPAP for 4 mo in patients with severe OSA who were free of comorbidities was associated with an improvement in early signs of atherosclerosis, with a reduction of carotid intima-media thickness, pulse-wave velocity, C-reactive protein and cetecholamines[22]. In addition, vascular response to hypoxia is diminished in patients with sleep apnea and can be also corrected with CPAP[23].

In a prospective observational study of ischemic stroke patients, those with an AHI ⩾ 20 who did not tolerate CPAP showed an increased risk of mortality compared to patients with moderate to severe OSA who tolerated CPAP[24]. However, no randomized controlled trials have been conducted to determine the value of CPAP treatment in stroke patients with SDB. For this reason, we designed a randomized controlled trial in which patients with ischemic stroke were assigned to early treatment with nasal CPAP (3-6 d after stroke onset) or conventional treatment[25]. The first learning from our study was that treating these patients with nasal CPAP in the acute stroke phase was feasible. The baseline characteristics of the 14 patients (19.7%) excluded from the study, because of refusal of nasal CPAP during hospitalisation were similar to those of the whole study population. The mean (SD) nasal CPAP use was 5.3 (1.9) h/night during a mean of 6.8 (0.6) nights/wk. The mean nasal CPAP pressure was 8.6 cm H_2O. A face mask was necessary in only four patients because of leaks, mainly due to facial palsy. The percentage of patients with neurological improvement 1 mo after stroke was significantly higher in the CPAP group than in controls (Rankin scale 90.9% *vs* 56.3%, OR = 5.8, $P < 0.01$; Canadian scale 88.2% *vs* 72.7%, OR = 2.8, $P < 0.05$). Early use of nasal CPAP seems to accelerate neurological recovery and to delay the appearance of cardiovascular events, although an improvement in patients' survival was not shown, perhaps because the follow-up period was not longer enough[25]. Therefore, the same group of patients was followed for a total of 5 years, and patients in the CPAP group had a higher survival free of cardiovascular events than controls[26]. Thus, we could suggest for the first time that early nasal CPAP therapy has some positive effect on long-term survival in patients with ischemic stroke and moderate-severe OSA[26].

The story of the relationship between SDB and stroke has not yet come to the end. There is sufficient evidence that this relationship makes sense and is going to be confirmed in future studies. However, for the present and future scenarios, pneumologists and neurologists especially those working in stroke units should work together to pursue in the establishment of a definitive relationship between sleep disorders and acute cerebrovascular events.

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REVIEW

Cytopathologic diagnosis of fine needle aspiration biopsies of thyroid nodules

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Abstract

Fine-needle aspiration (FNA) cytology is an important diagnostic tool in patients with thyroid lesions. Several systems have been proposed for the cyropathologic diagnosis of the thyroid nodules. However cases with indeterminate cytological findings still remain a matter of debate. In this review we analyze all literature regarding Thyroid Cytopathology Reporting systems trying to identify the most suitable methodology to use in clinical practice for the preoperative diagnosis of thyroid nodules. A review of the English literature was conducted, and data were analyzed and summarized and integrated from the authors' perspective. The main purpose of thyroid FNA is to identify patients with higher risk for malignancy, and to prevent unnecessary surgeries for benign conditions. The Bethesda System for Reporting Thyroid Cytopathology is the most widely used system for the diagnosis of thyroid FNA specimens. This system also contains guidelines for the diagnosis and treatment of indeterminate or suspicious for malignancy cases. In conclusion, patients who require repeated FNAs for indeterminate diagnoses will be resolved by repeat FNA in a percentage of 72%-80%.

Key words: Thyroid; Cytopathology; Nodule; Papillary cancer; Fine needle; Biopsy

Core tip: Fine-needle aspiration (FNA) cytology is widely used for the diagnosis of thyroid nodules, although cases with indeterminate results are not rare. We reviewed the English literature regarding Thyroid

Cytopathology systems in order to identify the most suitable methodology, taking into account our prospective as well. The Bethesda System for Reporting Thyroid Cytopathology is the most preferred system for the diagnosis of FNA specimens, which also contains guidelines for the diagnosis and treatment of indeterminate cases. Last but not least, repeated FNAs will lead to a diagnosis in 72%-80% of indeterminate cases where repeated FNAs were needed.

Misiakos EP, Margari N, Meristoudis C, Machairas N, Schizas D, Petropoulos K, Spathis A, Karakitsos P, Machairas A. Cytopathologic diagnosis of fine needle aspiration biopsies of thyroid nodules. *World J Clin Cases* 2016; 4(2): 38-48 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i2/38.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i2.38

INTRODUCTION

Thyroid nodules is a very usual clinical problem, as it is diagnosed in approximately 60% of the general population in Western countries[1]. However; less than 10% of them represent malignant tumors. Therefore, it is not prudent to remove every thyroid nodule we encounter in our medical practice. Fine-needle aspiration cytology (FNAC) has been widely adopted as a meticulous, secure and cost-effective method for the diagnosis of non-toxic thyroid nodules[1,2]. Its clinical utilization is significant, as it can define whether a recently emerged thyroid nodule should be managed expectantly or surgically, and can assist in selecting the appropriate surgical procedure when necessary[3].

Occasionally FNAC results can be inconsistent and can be a source of dispute among clinicians. The reason is that in approximately 10%-30% of cases, cytology is indeterminate and nondiagnostic[4]. Various diagnostic terminologies, including "indeterminate", "atypical", and "suspicious for malignancy," were used to describe these challenging cases[5]. Until recently there were no uniform criteria for the various diagnostic categories in thyroid cytopathology. This resulted in diagnostic inconsistencies among different laboratories and difficulty in communicating the implications of thyroid fine-needle aspiration (FNA) results both to clinicians (endocrinologists and endocrine surgeons) and laboratory doctors (pathologists and radiologists)[6]. In order to establish a standardized diagnostic terminology/classification system for reporting thyroid FNAC results, the National Cancer Institute (NCI) in the United States sponsored the NCI Thyroid FNA State of the Science Conference with a group of experts at Bethesda, MD, in October 2007[7]. This conference established the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), a 6-tiered diagnostic classification system based on a probabilistic approach[8,9]. Almost simultaneously, in Europe, the British Thyroid Association-Royal College of Physicians and the Italian Society for Anatomic Pathology and Cytopathology-International Academy of Pathology (SIAPEC-IAP) thyroid reporting systems, each comprised of 5 diagnostic classes, have been introduced[10,11]. In several countries the Cytological Communities have adopted the first system or the other, as there is still an ongoing dispute on whether the 5-tiered system or the 6-tiered system is more efficient[12].

In this review we analyze current literature regarding Thyroid Cytopathology Reporting systems trying to identify the most suitable and practical methodology to use in everyday clinical practice.

FNA procedures

The thyroid FNAs can be performed either by direct puncture after palpating the thyroid nodule, or more commonly under ultrasound guidance by dedicated thyroid specialists (endocrinologists, radiologists, or pathologists). Palpation-guided FNA can be performed when a thyroid nodule is easily palpable (> 1.0 cm in diameter) and rather solid. Ultrasound guidance is preferable than palpation-guided FNA for small nodules (< 1 cm), cystic lesions and when a prior FNA is non-diagnostic[13].

The thyroid nodules are aspirated 3 to 5 times with a 22-gauge or 25-gauge needle. From each FNA pass one to three smears are prepared and fixed in alcohol for Papanicolaou staining and air dried for Giemsa staining. Liquid-based preparation can also be made after a FNA pass, with the needle been rinsed in normal saline or ThinPrep solutions. As a result, 3 to 15 glass slides from each patient are taken and examined, which can be either Giemsa- or Papanikolaou-stained slides[14]. Regardless the staining method used, all slides with diagnostic material are used for the evaluation and clarification of each case.

CYTOLOGICAL CLASSIFICATION

The Bethesda system for reporting thyroid cytopathology

The six-tier diagnostic approach includes the following six categories[8,15]: (1) Disctrict of columbia (DC) Ⅰ Nondiagnostic or Unsatisfactory. These specimens demonstrate inadequate cellularity, poor fixation and preservation, obscuring blood or ultrasound gel, or a combination of the above factors. Inadequate cellularity is defined as the presence of less than 6 groups of well-preserved follicular cells on each of at least two slides; (2) DC Ⅱ Benign (Figure 1). This category includes the diagnoses of nodular goiter, nodular goiter with hyperplastic nodules, colloid nodules, cyst contents with/without benign follicular cells, and lymphocytic thyroiditis; (3) DC Ⅲ Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (Figure 2). This category is reserved for aspirates with borderline cellularity and is subdivided into two subcategories. One subcategory includes cases with a microfollicular pattern and minimal colloid, that is, follicular lesion of undetermined significance (FLUS). The

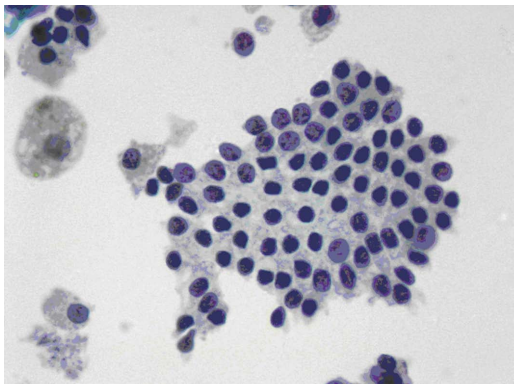

Figure 1 Follicular cells arranged in a flat sheet, colloid and pigment-laden macrophages (× 40 pap stain on ThinPrep slide) (diagnostic categories Ⅱ).

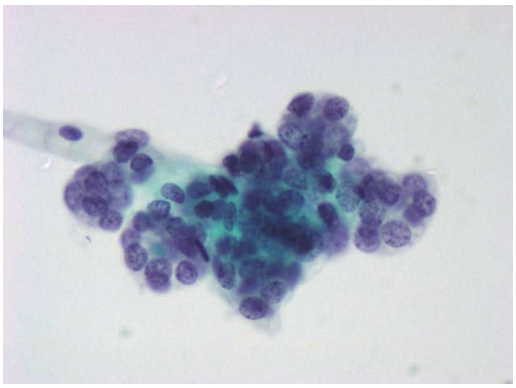

Figure 2 Crowded macrofollicles with mild irregularities in nuclear membrane and prominent nucleoli in a specimen with scant colloid (× 40 pap stain on ThinPrep slide) (diagnostic categories Ⅲ).

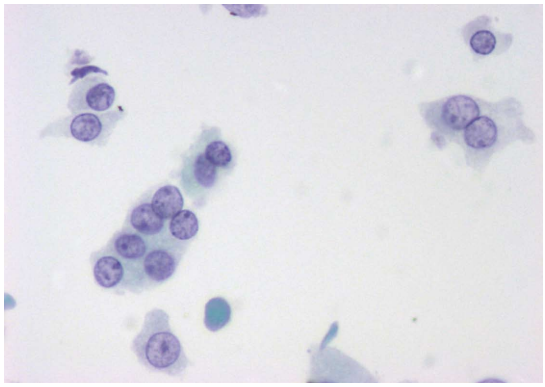

Figure 3 A cellular specimen composed of Hürthle cells arranged in loosely cohesive sheets or isolated in a case diagnosed as Hürthle cell adenoma (× 40 pap stain on ThinPrep slide) (diagnostic categories Ⅳ).

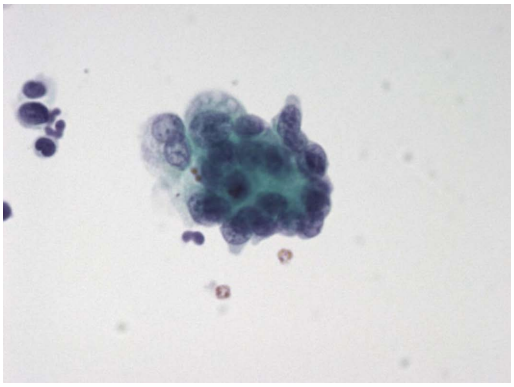

Figure 4 Presence of cell group with nuclear crowding, increased nuclear-cytoplasmic ratio, irregularities in nuclear membrane and micro-nuclei (× 40 pap stain on ThinPrep slide) (diagnostic categories Ⅴ).

second subcategory includes cases with nuclear atypia, such as the presence of occasional nuclear grooves, nuclear crowding, and abnormal chromatin pattern, which are characteristics of papillary carcinoma (PTC). This subset of patients could benefit form a repeat FNA; (4) DC Ⅳ Follicular Neoplasm or Suspicious for a Follicular Neoplasm. This category refers to cellular specimens with abundant follicular cells arranged in a microfollicular pattern with minimal colloid. The differential diagnosis includes hyperplastic adenomatous nodules, follicular adenoma, follicular carcinoma, and follicular variant of PTC, where the nuclear features remain ill defined. This category also includes cases with a predominant population of Hurthle cells; these cases are labelled Hurthle cell neoplasm (Figure 3). The differential diagnosis for the latter includes hyperplastic adenomatoid nodule with Hurthle cell change, Hurthle cell adenoma, and Hurthle cell carcinoma; (5) DC Ⅴ Suspicious for malignancy. This category includes specimens with features characteristic of a malignant neoplasm, which are quantitatively or qualitatively insufficient to make a definitive diagnosis of malignancy (Figure 4). These features could be intranuclear inclusions, nuclear grooves, or psammoma calcifications; (6) DC Ⅵ Malignant (Figures 5-7). This category includes specimens with unequivocal cytologic evidence of a malignant neoplasm. Herein, all histological types of thyroid carcinoma are included: PTC and its variants, medullary carcinoma, anaplastic carcinoma, lymphoma, and metastatic lesions.

The European systems for reporting thyroid cytopathology

In 2007 the Royal College of Pathologists introduced a new thyroid FNA reporting system, which was based on the existing United Kingdom terminology, but with some alterations, like new subcategories (*i.e.,* "c" for cystic lesions, "a" for atypia, "f" for follicular neoplasm). These alterations were made in order for the British system to be analogous to the BSRTC[11,16], although in other countries these modifications have not be totally embraced. Furthermore, various other thyroid FNA reporting systems have been created, in which the experiences of the pathologists and/or associated risks of malignancy have been taken into account. The most widely known is the SIAPEC-IAP thyroid reporting system, which is also consists of 5 diagnostic classes[12].

Both the European and the American systems are considered as a significant accomplishment and hold the promise for better classification of thyroid FNA

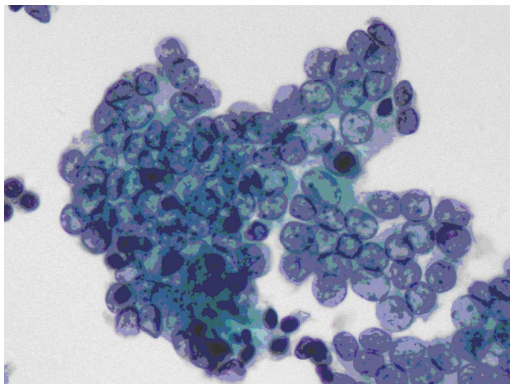

Figure 5 Flat sheets showing enlarged, pale nuclei with finely granular chromatin of a papillary Ca case (× 40 pap stain on ThinPrep slide) (diagnostic categories Ⅵ).

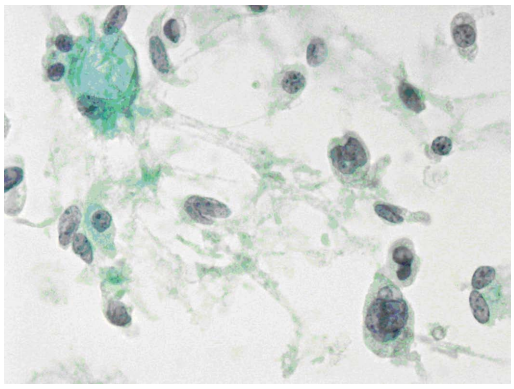

Figure 7 Tumor cells with distinct granules with eccentric nuclei. The nuclear chromatin appears as "salt and pepper type" in a medullary carcinoma case (× 40 pap stain on ThinPrep slide) (diagnostic categories Ⅵ).

results[6,10,11,17,18]. The main difference between the 5-tiered system and the 6-tiered system is that the DC Ⅲ [atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)] category is included only in the 6-tier system, a category with considerable prevalence, as it is calculated 6%-7% according to various statistics[14]. Bongiovanni *et al*[14] analyzed the differences between the 5-tiered and the 6-tiered diagnostic systems for reporting thyroid cytopathology, based in a large series of 7686 thyroid FNA specimens, collected from 3751 patients from several institutions from Italy, Switzerland, and the United States. They found that apart from the TIR Ⅲ category, for the TIR 1/DC Ⅰ (unsatisfactory/nondiagnostic) category the percentage of cases in the 5-tiered system was greater than twice the percentage of cases in the 6-tiered system (7.5% *vs* 3%). There was also a great difference regarding the percentage of the cases classified into the TIR 2/ DC Ⅱ (benign) category (83.9%) compared with approximately half (55.4%) of the cases in the 6-tiered system. However, the percentage of the cases classified into the TIR 3/DC Ⅳ (follicular proliferation/neoplasm) category was substantially smaller (4.6%) in the 5-tiered system compared with the 6-tiered system (23.8%). Moreover, a lower percentage of cases in the European

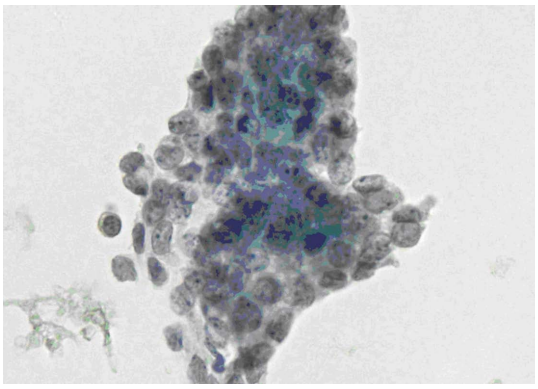

Figure 6 Enlarged follicular cells arranged in monolayer sheets and follicular groups with nuclear elongation and chromatin clearing in a follicular variant of PTC case (× 40 pap stain on ThinPrep slide) (diagnostic categories Ⅵ).

system was placed into the TIR 4 and TIR 5 categories as well, compared with the American system.

The management of each case derives from the category that is classified. Therefore, the DC Ⅲ (AUS/FLUS) cases are managed conservatively with repeat FNAs, whereas the DC Ⅳ, DC Ⅴ, and DC Ⅵ cases, and TIR 3, TIR 4 and TIR 5 cases respectively, are managed operatively, with thyroid lobectomy or total thyroidectomy. In addition, obtaining adequate material at FNA is a very important issue, as the rates of malignancy observed in the nondiagnostic categories of both reporting systems are very high[14].

The necessity for the DC Ⅲ (AUS/FLUS) category

The majority of the thyroid FNA specimens, in the range of 60% to 70%, are classified as benign, whereas approximately 20% to 30% fall into the 3 categories of suspicious for follicular neoplasm, suspicious for malignancy, and malignant[19]. The remaining 10% of cases represent a significant subset of thyroid specimens with some form of AUS/FLUS. Such atypia may result from a variety of benign cellular changes, but in some cases may reflect an underline malignancy which has been suboptimally sampled or has intermediate diagnostic features[20-22].

The AUS/FLUS category in the Bethesda system, represents aspirates that contain follicular, lymphoid, or other cell types with architectural and/or nuclear atypia that is more pronounced than that observed in benign lesions yet not sufficient to be characterized as suspicious for follicular neoplasm (SFN), or suspicious for malignancy[10]. The authors of the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) recommended that the DC Ⅲ (AUS/FLUS) category should not exceed 7% of the thyroid FNA diagnoses, and the risk of malignancy in this category should be in the range of 5% to 15%[23].

These indeterminate aspirates may present with architectural atypia or nuclear atypia[21]. Architectural atypia may present in smears with paucity of cells, which contain a few microfollicles, trabeculae, or crowded

groups. Several patterns of nuclear atypia may be also present without being quantitatively and/or qualitatively sufficient for the interpretation of "suspicious for malignancy". These include hypocellular smears with extensive cystic degeneration with rare follicular cells with nuclear atypia indicative of PTC. In some cases more diffuse but mild nuclear changes may exist with nuclear enlargement, crowding, and pallor, but without other characteristics, such as nuclear contour irregularities, grooves and nuclear pseudoinclusions, suggestive of a PTC.

Another pitfall encountered with cystic thyroid nodules are the atypical cyst-lining cells[24]. Benign cyst-lining cells are typically polygonal or fusiform with abundant cytoplasm, well-defined cellular borders, sometimes enlarged, grooved nuclei, and small distinct nucleoli. The isolated cyst-lining cells in thyroid aspirates are often difficult to distinguish from PTC. For that reason the aspirate is then classified as AUS/FLUS to indicate the uncertainty of the findings.

The malignancy rate of the AUS/FLUS category is estimated to be between 5% and 15%[10], which is intermediate between that of the benign category (0%-3%) and that of the SFN category (15%-30%). The most common malignant diagnosis made after surgery in cases initially classified as AUS/FLUS is PTC, usually of the follicular variant (PTC-FV)[24,25]. Since the malignancy rate of this category is quite high, TBSRTC recommends that most patients undergo a repeat thyroid FNA within 3 to 6 mo, in order to define the nature of atypia[24,26]. However, in almost 20% to 28% of AUS/FLUS cases, a repeat thyroid FNA will again be characterized as AUS/FLUS[27,28]. In a study by Teixeira *et al*[29] the overall incidence of malignancy in the FNA-biopsied nodules characterized as FLUS was 16.2%, a higher value than the suggested 5% to 15%[10,29-31]. In a large study with 1382 cases in a community practice setting, in the United States, Wu *et al*[32] diagnosed AUS in 27% of cases, ranging from 10% to 47% among pathologists participating in the study. The risk of malignancy of AUS/FLUS was only 6%, a quite lower value than the one reported elsewhere. In this study the AUS category was further subdivided into HCLUS (atypical cells rule out Hurthle cell neoplasm) and FLUS. The risk of malignancy in the HCLUS category was significantly lower than in the other subtypes of AUS. Many of the HCLUS cases did not show any of the above features and were proved to be benign adenomas. Such patients were followed clinically with periodic physical and sonographic examinations. Renshaw noted that a Hurthle cell neoplasm demonstrating one of the following features: Small cell dysplasia, large cell dysplasia, severe nuclear crowding, and dishesive cellular pattern is usually associated with a high risk of malignancy[33].

The suspicious for malignancy category

Most primary thyroid malignancies with the exception of follicular and Hurthle cell carcinomas have unique cytological features which can differentiate primary malignancies from other thyroid lesions. However, there are cases with diagnostic uncertainty due to suboptimal sampling or preservation, and overlapping cytomorphologic features with other thyroid conditions. A specimen is considered as "suspicious for malignancy" (SFM), when some features of malignancy (usually PTC features) exist, but the findings are not sufficient for a definitive diagnosis[9]. These indeterminate results imply surgeons to consider alternative therapies (*e.g.*, thyroid lobectomy with intraoperative frozen section).

SUSPICIOUS FOR PTC

Pattern A (patchy nuclear changes pattern)

In this pattern benign follicular cells are detected, along with cells with nuclear enlargement, nuclear grooves, nuclear membrane irregularity, and/or nuclear molding, usually without any trace of intranuclear inclusions.

Pattern B (incomplete nuclear changes pattern)

In this pattern the nuclear enlargement is generalized in mild-to-moderate degree with evident nuclear grooves and mild nuclear pallor.

Pattern C (sparsely cellular specimen pattern)

In this pattern many features of PTC are found, but it is sparsely cellular.

Pattern D (cystic degeneration pattern)

In this pattern cystic degeneration with hemosiderin-laden macrophages is present. There are also sheets of follicular cells with large pale nuclei and some with nuclear grooves, but without intranuclear inclusions. Moreover, large, atypical, "histiocytoid" cells with enlarged nuclei and abundant vacuolated cytoplasm usually coexist.

Although these nuclear alterations are usually disseminated, they are mild and incomplete. These changes are not pathognomonic, as they are frequently detected in some PTCs, especially in the follicular variant, and in benign lesions as well, such as follicular adenomas. For that reason these findings are best interpreted as SFM.

Cystic degeneration also is often found. Cyst lining cells are usually elongated, containing pale chromatin, with sparsely found intranuclear grooves, large nucleoli, and always associated with hemosiderin-laden macrophages and benign-appearing macrofollicle fragments. The spindle-shaped morphology of these cells is helpful in distinguishing these cells from PTC[24,34].

SUSPICIOUS FOR MEDULLARY CARCINOMA

The cellular sample is typically monomorphic, although some specimens may appear pleomorphic; the cells are usually small or medium-sized, noncohesive, and contain an eccentrically located nuclei[35]. There may be small fragments of amorphous material-colloid *vs*

amyloid. The sensitivity of thyroid FNA for medullary thyroid carcinoma (MTC) is considered high, actually it is higher than the sensitivity of FNA for PTC[36]. However in doubtful cases definitive diagnosis can be made if sufficient material is available for immunocytochemical stains, or if it is known that the patient has an elevated serum calcitonin level.

Suspicious for lymphoma

The sample is composed of numerous monomorphic lymphoid cells. In other cases it is sparsely cellular and contains atypical lymphoid cells. The difficulties in securing diagnosis of a diffuse large B-cell lymphoma derive from the inadequate sampling technique and/or insufficient preservation of the specimen. On the other hand a definitive diagnosis of a low-grade lymphoma (usually a MALT lymphoma) is even more difficult. The diagnosis of a MALT lymphoma of the thyroid requires the use of immunophenotyping by flow cytometry or immunocytochemistry[9,37].

Management

Review of the literature suggests a malignancy rate of 55%-75% for the suspicious category[8]. Therefore the diagnosis "SFM, suspicious for thyroid carcinoma" is an indication for surgery. The contribution of intraoperative frozen section after a suspicious FNA diagnosis is questionable, as Lee *et al*[38] have demonstrated that preoperative FNA has a higher sensitivity than frozen section in detecting PTC. Another diagnostic option for patients with repeat ultrasonography-guided FNA of thyroid nodule with non-diagnostic cytology results, would be the utilization of ultrasonography-guided core needle biopsy[39]. This technique is conclusive for the majority of cases suspicious for PTC, lymphoma, or follicular neoplasm after previous incomplete FNA results.

For patients with large tumors (> 4 cm), the best approach could be a total thyroidectomy, considering the fact that large tumors have an elevated risk of malignancy[40].

Apart from imaging studies, serological or immunohistochemical studies can be used to secure diagnosis, when the FNA indicated "suspicious for MTC" or "suspicious for lymphoma". For example, increased serum calcitonin levels and/or strong immunoresponce of chromogranin which is disclosed after multiple FNA tests can indicate the diagnosis of a medullary carcinoma.

PAPILLARY THYROID CARCINOMA

PTC accounts for 80% of all thyroid malignancies and occurs more often in women with a 3:1 female-to-male ratio, with a mean age at presentation 30-40 years. It usually behaves as an indolent malignant tumor; however, an aggressive clinical course with decreased survival has been reported in some histologic variants of PTC[41]. PTC most commonly metastasizes *via* lymphatics. Distant metastases seldom occur, but may develop in 20% of cases in late stage. The most common sites are the lungs, bone, liver and brain. The prognosis of this tumor is good; death due to PTC is rare.

At low magnification, aspirates of PTC are typically cellular, epithelium-rich structures. Papillary structures are not as common as it was believed, because intact papillae are often too large to enter the fine needle or are disrupted during the preparation of the smears. However, some three dimensional structures that resemble the epithelial tips of papillae without the fibrovascular cores can be seen[35].

The cytological diagnosis of PTC is based mainly on the characteristic nuclear morphology. The FNA specimen of this neoplasm is usually cellular and shows neoplastic cells arranged in papillary groups, or clusters, or as single cells in a background of thick colloid, nuclear or calcific debris, macrophages and stromal fragments[41] (Figure 4).

The individual tumor cells are enlarged, oval in shape with eosinophilic cytoplasm; the nuclei show elongation, oval shape, membrane thickening, chromatin clearing, grooves, and inclusions. The nucleoli are usually small and eccentric; however, rare oncocytic variants of PTC can show prominent nucleoli. Nuclear grooves become an important diagnostic feature when associated with an oval, enlarged nucleus with fine chromatin[41]. However, nuclear grooves can be seen also in several thyroid diseases such, as Hashimoto's thyroiditis, multinodular goiter, Hurthle cell tumors and medullary carcinoma[42,43].

Psammoma bodies are occasionally seen in some aspirates, most possibly arising from calcification of epithelial tips. The presence of true psammoma bodies with concentric laminations is highly suggestive of PTC; however the presence of psammoma bodies in cystic thyroid lesions is not diagnostic. Consequently it is essential to distinguish this form of atypical calcification from true psammomatous calcifications with their concentrically laminated microscopic appearance[35].

PTC VARIANTS

Follicular variant

This is the most common variant of PTC and is characterized by a predominantly follicular architecture. Since the PTC-FV variant represents one of the most common causes of a false negative diagnosis of PTC, it is important to distinguish this PTC variant from other benign conditions, such as a follicular neoplasm or adenomatous nodule.

FVPTC is characterized cytologically by the paucity of diagnostic nuclear features. The FNA specimens show enlarged follicular cells arranged in monolayer sheets and follicular groups in a background of thin and thick colloid (Figure 6). The tumor cells show nuclear elongation, chromatin clearing, but nuclear grooves and inclusions are rare[40]. Because the nuclear changes of FVPTC are subtle, the majority of cytologic samples are often diagnosed as suspicious for PTC.

Cystic variant

Among thyroid malignancies, PTC has the highest propensity to appear cystic, as 10% of the PTC specimens are entirely cystic. In FNA specimens of this variant, the cancer cells appear more profuse, granular or vacuolated compared to regular PTC. The nuclei are enlarged, with usually an oval or irregular shape, and include intense nuclear grooves and inclusions. This variant is sometimes difficult to diagnose, because in some cases the characteristic neoplastic cells are sparsely evident in the mass. As a result they may be not diagnosed through the FNA test, resulting in a false-negative test[44].

Oncocytic variant

This variant of PTC is not common, but it is important to be recognized as it may be confused with a Hurthle cell neoplasm[44]. The specimen is usually cellular with polygonal cells in loose papillary clusters with abundant eosinophilic cytoplasm. The nuclei have conventional PTC nuclear features that distinguish it from Hurthle cell neoplasms[35].

Warthin-like variant

This PTC variant is a circumscribed thyroid tumor with papillary architecture and lymphoid follicles that mimics a Warthin tumor of the parotid gland. FNAs contain oncocytic cells with abundant granular cytoplasm, conventional nuclei, a papillary architecture, and a lymphoplasmacytic background. The neoplastic cells resemble Hurthle cells but have diagnostic nuclear features of PTC. Because of the mixture of oncocytes with lymphocytes on smears, this tumor should be distinguished from Hashimoto thyroiditis or a follicular lesion with oncocytic changes[44].

Tall cell variant

The tall cell variant of PTC is an important subtype with a potentially aggressive clinical course. It usually affects the elderly population, and often presents as a large and bulky tumor with extrathyroidal extension and metastases. The diagnosis of this variant as a PTC is relatively easy, due to the numerous papillae and the coexisting intranuclear inclusions. The cancer cells are also elongated, with a height-to-weight ratio of at least 3:1. The cells have abundant pink cytoplasm, basally located nuclei and nuclear features of conventional PTC. These cells constitute more than 50% of tumor volume[44].

Columnar cell variant

This is an aggressive variant of PTC characterized by the presence of crowded, stratified clusters of elongated cells resembling cells from a colonic adenoma. The nuclei are hyperchromatic, uniform in size and shape, and with indinstinct nucleoli. The neoplastic cells show a greater cell height than the tall cell variant and lack the obvious nuclear features of PTC. Due to the fact that the nuclei of this variant are darker than those of the regular PTC, the neoplastic cells of this variant may be mistaken for benign respiratory epithelial cells, or a colorectal neoplasm. Additionally an immunohistochemical panel, including thyroglobulin, TTF1, and CDX2 may help in the differential diagnosis of such difficult cases.

Hyalinizing trabecular tumor

It is not widely agreed whether this neoplasm is a variant of PTC or not, although it seems to have the same RET gene rearrangements as PTC. The hyalinizing trabecular tumor is an uncommon malignancy originating from follicular cells, with certain unique features, such as trabecular growth, marked intracellular hyalinization along with nuclear grooves and pseudoinclusions. In some cases psammoma bodies may be present[35,44].

Management

In general, patients diagnosed with FNA test as having PTC, are usually managed operatively, but the final decision of the type of resection (lobectomy *vs* total thyroidectomy) depends on numerous coexisting factors. Specifically, the ultrasound image of the malignant nodule, as well as the patient's general condition and age and other comorbidities should be taken into account when planning surgery.

The standard management of PTCs greater than 1 cm is total, or near-total thyroidectomy followed by radioactive iodine (^{131}I) therapy to ablate residual thyroid tissue. After this therapy the patient's serum thyroglobulin levels should fall to undetectable levels. Since recurrent PTC typically secretes thyroglobulin, serum monitoring of thyroglobulin serves as a useful tumor marker for recurrent PTC[35].

The management of cases with papillary microcarcinomas, *i.e.*, tumors less than 1.0 cm in diameter, is still controversial. These small tumors may be incidentally discovered in glands removed for other reasons, they are treated with thyroidectomy; these patients usually do not need systemic ^{131}I therapy and do not require a second-stage completion thyroidectomy.

MTC

Definition

MTC was first described by Horn *et al*[45] in 1951, and it was first recognized as a unique clinicopathological entity by Hazard *et al*[46], in 1959. In 1966 Williams demonstrated that this tumor derives from the parafollicular cells, known also as calcitonin-producing C cells, which have an ectodermal neural crest origin[47].

MTC represents 3%-12% of thyroid cancers, the majority of which are sporadic. However, in almost 25%-30% of cases, MTC is inherited, and is associated with one of three familial syndromes: Multiple endocrine neoplasia (MEN) syndrome type 2A (Sipple's syndrome), MEN type 2B (mucosa neuroma syndrome or Gorlin's syndrome), and familial MTC[35]. The inherited forms are characterized by an autosomal dominant mode of inheritance and are associated with point mutations in

the RET proto-oncogene on chromosome 10.

Patients with the sporadic forms of MTC or the familial MTC are most often middle-aged (mean age 50 years old), except in familial cases, in which they are relatively younger. Patients with sporadic MTC present with a solitary, circumscribed thyroid nodule, usually in the middle to upper-outer half of the thyroid gland. Medullary carcinoma is highly metastatic, as tumor cells can be disseminated through hematogenous and metastatic routes to numerous sites, including cervical lymph nodes, liver, lung, bone, and adrenal glands. Almost all patients with MTC have a significantly elevated serum calcitonin level, and in some cases these tumors can produce substances that can lead to paraneoplastic syndromes[35,44].

Diagnostic cytology

The FNA aspirates of an MTC are usually composed of numerous cells, either presenting in cell aggregates or as a mixture of non-cohesive cells. Characteristically, distinct granules (calcitonin granules) are spotted in the cytoplasm of the cancer cells, as well as eccentric nuclei, indicating a plasmacytoid appearance to the tumor cells. The nuclear chromatin is similar to that seen in other neuroendocrine tumors, *i.e.,* "salt and pepper type" (Figure 7). Intranuclear inclusions and multinucleated cells have been reported. Therefore this tumor may mimic other thyroid tumors, such as Hurthle cell neoplasms, PTCs, anaplastic carcinomas, and metastatic tumors. Immunohistochemistry test for specific biomarkers (*i.e.*, calcitonin, thyroglobulin) will easily distinguish MTC from other thyroid malignancies. Amyloid can be observed in close association with tumor cells, and can be distinguished from the thick colloid of PTC by performing a Congo-red stain. The diagnosis of MTC can be confirmed by simply measuring serum calcitonin levels, which are markedly elevated in the majority of cases (> 10 pg/mL)[48].

UNDIFFERENTIATED (ANAPLASTIC) THYROID CARCINOMA

Definition

Undifferentiated (anaplastic) thyroid carcinoma (UTC) is an extremely aggressive thyroid malignancy with a very poor prognosis. It generally affects elderly patients presenting as a firm mass rapidly growing in the neck infiltrating extrathyroidal tissues, such as muscle, trachea, esophagus, skin, bone and cartilage[49]. Half of patients present with significant compression of the upper respiratory and the digestive tract in the neck, resulting in dyspnea, hoarseness, dysphagia, and pain. Lymphadenopathy is also present in one quarter to half of patients, whereas the lungs is the most common site of metastases[49,50]. For most cases surgical resection is not an effective treatment and only palliative therapies are used. Prognosis is dismal with a mean survival of 2.5 to 6 mo and an overall 5-year survival of 0% to 14%.

Cytology

The aspirates from anaplastic carcinoma do not pose any diagnostic difficulties. They can be sparsely cellular, because of the marked fibrosis and hyalinization encountered in some cases[19,51]. They can be readily classified as malignant due to nuclear pleomorphism, chromatin clumping, necrosis, atypical mitoses and other malignant features[40]. Pan-keratin is the most reliable positive immunostain in UTCs, acquiring an expression ranging from 50% to 100%. Vimentin immunoexpression is also a common finding[52]. When evaluating an undifferentiated carcinoma using immunocytochemistry a basic immunopanel should include cytokeratins, calcitonin, leucocyte common antigen, carcinoembryonic antigen, thyroglobulin, chromogranin, and TTF-1. Some cases may present with diagnostic difficulty if the specimen consists mainly of necrotic debris or if the tumor is extremely sclerotic (the paucicellular variant)[40,53].

Management

Because of its aggressive, infiltrative nature, patients with an undifferentiated carcinoma often require a tracheostomy as an emergency procedure. If the tumor is small and confined to the thyroid, thyroidectomy may be feasible; however, in most cases the tumor extends outside the thyroid gland preventing adequate resection[35]. Chemotherapy or radiotherapy usually cannot change the dismal prognosis of this cancer.

Molecular diagnosis

Since there is a considerable proportion of patients with a thyroid nodule who remain undiagnosed with FNA, molecular biology could be very helpful at that point. Research is directed to the identification of molecular markers that, in conjunction with FNA, can identify patients with a malignant nodule.

BRAF mutation has become a specific marker for PTC and its variants[54]. BRAF testing has been coupled successfully with the Bethesda Thyroid FNA classification system to offer molecular quality assurance on positive samples, as well as a diagnostic upgrade on samples of indeterminate diagnostic categories, such as AUS/FLUS and SFN/SHN[54]. The rate of malignancy in FNA-BRAF positive nodules has been shown to be 99.8%[55]. BRAF is not usually found in the follicular variant of papillary thyroid carcinoma, but is increasingly detectable in each step of dedifferentiation, including tall cell tumors and anaplastic cancer. It is a point of great significance that Ohori *et al*[56] found a greater percentage of BRAF-mutated (V600E, K601E, and others) cases in the AUS/FLUS and SFN/SFN categories, rendering BRAF mutational testing a useful predictor of PTC diagnosis in these indeterminate cases. While the V600E and K601E mutations were almost equally observed in the AUS/FLUS category, there was a slight predominance of K601E mutation in SFN/SHN category. In these SFN/SFN and AUS/FLUS cases with the K601E mutation, the cytomorphology of the PTC specimens prevented a

more definitive diagnosis, in contrast to cases where the V600E mutation was observed, whether the diagnosis resolved to a classic (CL) subtype, tall cell variant (TCV) subtype, or a solid (SD) PTC diagnosis. The high sensitivity rate, as well as the high negative prognostic value of BRAF testing in AUS/FLUS and SFN/SFN categories have been also demonstrated by Alexander *et al*[57].

A full molecular panel of BRAF, RAS, RET/PTC and PAX8PPARγ offer additional diagnostic value[58]. However, this requires additional FNA passes or residual cellular material from the cytologic sample. Cantara *et al*[59] evaluated this panel of tumor-associated mutations in thyroid FNA samples. The above panel correctly identified cancer in 78.2%, whereas cytology identified 58.9% of the thyroid cancers. It also predicted cancer in the majority of indeterminate samples, as well as of the suspicious for cancer samples. Interestingly all predicted cancer proved to be papillary thyroid carcinoma in the final histology[59]. Moses *et al*[60] also examined the clinical utility of the above panel in thyroid FNA biopsies. When this panel was used for specimens with indeterminate cytology, sensitivity was 27%, specificity was 95%, positive predictive value was 66%, and negative predictive value was 78%[60]. In addition, Ohori *et al*[61] investigated the utility of the above panel in specimens classified as FLUS. The molecular testing proved to have a high specificity, although the sensitivity was quite low (60%). Despite the fact that not all PTC were detected by this panel, a positive molecular test helped to refine the FLUS cases into high-risk and low-risk categories[61].

Extensive research is going on in this field; an important step for the introduction of new molecular markers in the diagnosis of molecular tumors could be the clinical testing of FNA samples in large multicenter trials.

CONCLUSION

Thyroid FNA is a well established procedure used in the preoperative diagnosis of thyroid nodules. It allows classification of nodules as benign or malignant, and patients with malignant nodules are scheduled for surgery. The main purpose of thyroid FNA is to stratify higher risk patients for surgery, and to prevent unnecessary surgeries for benign conditions.

TBSRTC provides a uniform 6-tier system on thyroid FNA for pathologists to communicate with clinicians. Each diagnostic category is associated with a specific risk of malignancy and a recommendation for management.

The TBSRTC classifies thyroid follicular lesions with microfollicle predominance and lack of colloid into the suspicious for follicular neoplasm category. This system allows patients with FNAs showing focal atypia to undergo repeat aspiration prior to surgery. Therefore, in the majority of patients in the AUS/FLUS category (72%-80%) the diagnosis will be resolved by repeat FNA, although 20%-28% of them will have AUS/FLUS on the repeat aspirate and thus require surgery.

A malignant thyroid FNA diagnosis accounts for 4%-8% of all thyroid FNAs, the majority of which are PTCs, and these patients will require thyroidectomy[53]. The use of molecular markers can further increase the diagnostic value of FNA samples for the detection of thyroid cancer.

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CASE REPORT

Safety and efficacy of anti-tumor necrosis factors α in patients with psoriasis and chronic hepatitis C

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Abstract

Up to date, in literature, it is still debated the role of anti-tumor necrosis factors (TNF)-α treatments in hepatitis C virus (HCV) patients. TNF-α performs a lot of functions, it is an important pro-inflammatory cytokine and it is involved in the host's immunity. Since TNF-α is implicated in the apoptotic signaling pathway of hepatocytes infected by HCV, anti TNF-α therapy may increase the risk of viral replication or their reactivation. However the treatment of anti TNF-α could have a healthful role because TNF-α appears to be engaged in the pathogenesis of liver fibrosis, inducing apoptotic pathways. We describe the case of a patient with plaque-type psoriasis and concomitant chronic HCV, who was treated successfully with anti-TNF agents simultaneously to cyclosporine without sign of reactivation of HCV and increase of liver enzymes. Our personal experience shows that anti-TNF-α agents are not only effective but also safe. Furthermore the combination therapy of cyclosporine and anti-TNF-α appears to be well-tolerated and able to reduce the amount of liver enzymes as well as HCV-viral-load. However systematic, large-scale studies with long follow-ups will be needed to confirm our results, in association with close liver function monitoring.

Key words: Hepatitis C virus infection; Cyclosporine; Psoriasis; Safety; Anti-tumor necrosis factors-α agents

Core tip: Our paper reports a patient with plaque-type psoriasis and concomitant chronic hepatitis C virus (HCV), focusing on the safety and efficacy of cyclosporine therapy and anti tumor necrosis factors-α agents. This therapeutic association is also able to decrease liver enzymes as well as HCV load with

general clinical improvement. Our topic may be useful in the clinical setting of patients with simultaneous severe psoriasis and chronic HCV infection.

Salvi M, Macaluso L, Luci C, Mattozzi C, Paolino G, Aprea Y, Calvieri S, Richetta AG. Safety and efficacy of anti-tumor necrosis factors α in patients with psoriasis and chronic hepatitis C. *World J Clin Cases* 2016; 4(2): 49-55 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i2/49.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i2.49

INTRODUCTION

Psoriasis is a chronic inflammatory disorder, showing an incidence in the worldwide population of 2%-3%, where the genetic predisposition plays a pivotal role[1,2]. Typically it shows well-bordered erythemato-squamous patches and plaques, often covered by a characteristic silvery white scale formed by the hyperproliferation of epidermal keratinocytes. In addition itching and burning occur together with the clinical manifestations of the disease, compromising the patient's quality of life[3-5].

According to the literature, in psoriatic patients, above all in the ones with a moderate and severity psoriasis, there is an increased risk of cardiovascular and metabolic disorders including diabetes mellitus, hypertension, obesity, dyslipidaemia, non-alcoholic fatty liver disease and arthritis[6,7].

In the last decade, the addition of tumor necrosis factors (TNF)-α antagonists has introduced new therapeutic perspectives for effective treatment of psoriasis and psoriatic arthritis. These treatments decrease the disease activity, also limiting and improving the pathological articular involvement. However, at the same time, TNF-α is also a critical cytokine implicated in the host's defence against infective pathogens, performing a key function in the management of viral infections[8].

Consequently, the inhibition of the TNF-α pathway is supposed to increase the susceptibility to various infections, including viral diseases as well as their reactivation and immune response by recruiting and activating macrophages, natural killer cells, T cells and antigen-presenting cells[9].

According to these observations, patients qualified for anti-TNF-α therapy require to be carefully assessed about possible infections, in particular, positive medical history for hepatitis B virus (HBV) and/or chronic hepatitis C virus (HCV).

However, to date, the safety of anti-TNF-α agents in HCV patients with psoriasis is quite restricted and controversial[10-13].

The current case describes our personal experience with TNF-α blockers in the treatment of a patient with plaque-type psoriasis and concomitant chronic HCV infection, evaluating their efficacy and safety.

CASE REPORT

A 47-year-old man was diagnosed with an moderate-severe plaque-type psoriasis ever since 7 years. His medical history included familiarity for psoriasis and chronic hepatitis C infection (genotype 4) first diagnosed in 1993. The patient received combined treatment with Peg-interferon (INF)-α-2a and ribavirin which he continued for 24 wk. At the time of the diagnosis, HCV infection was under control, with a quantitative RNA PCR value of 3.02 × 105 IU/mL. Laboratory evaluation revealed a moderate increase both in erythrocyte sedimentation rate (44 mm/H) and in liver enzymes [aspartate aminotransferase (AST): 78 U/L; alanine aminotransferase (ALT): 80 U/L; gamma glutamyl transferase (γ-GT): 60 U/L]. The ultrasonic imaging of the liver showed moderate hepatomegaly with sharp and diffuse dishomogenity and minimal steatosis.

Assessment of cryoglobulins, complete blood count, total protein, albumin, total cholesterol, prothrombin time, blood urea nitrogen (BUN), creatinine, and urine examination were also performed.

His baseline Psoriasis Area and Severity Index (PASI) score was 11.5 and Dermatology Life Quality Index (DLQI) was 16. Treatments with several different topical therapies for psoriasis, including corticosteroids, vitamin D derivatives (calcipotriol, calcitriol or tacalcitol) were ineffective. Joint ultrasound showed no signs of psoriatic arthropathy; chest X-ray and quantiferon tb gold were negative and the patient started 4 mg/kg per day cyclosporine (Figure 1). At the first follow up after 12 wk of treatment the patient showed a PASI score improvement (2.7) with a reduction of DLQI. At the same time his HCV RNA status remained unaltered.

At week 48 we observed an increase of BUN, creatinine and electrolytes, so we decided to reduce cyclosporine to a dose of 200 mg/d. However after further 4 wk the patient showed a worsened PASI score of 22.8 and DLQI 16 (Figure 2). At week 6, the patient began the first biological treatment with Etanercept at the dose of 50 mg weekly and at week 12 the PASI and DLQI were improved. Furthermore even if quantitative HCV RNA remained stable, we detected an increase of liver enzymes with the following values: AST: 99 U/L, ALT: 88 U/L and γ-GT: 99 U/L (Figure 3).

Etanercept was discontinued and the patient was started on intravenous anti TNF-α, infliximab, administration. At week 16 the liver enzymes decreased (AST: 60 U/L, ALT: 78 U/L, γ-GT: 96 U/L) while PASI score and HCV RNA maintained stable (Figure 4).

Since cyclosporine was discontinued because of kidney toxicity, Etanercept because of hepatic toxicity and clinical inefficacy and infliximab was stopped due to clinical failure, the patient was administrated the third anti TNF-α, that is adalimumab. At week 12 of treatment PASI score increased again whereas liver indexes were further restricted and HCV RNA serum levels decreased significantly (102 × 10^6 IU/mL) after 3

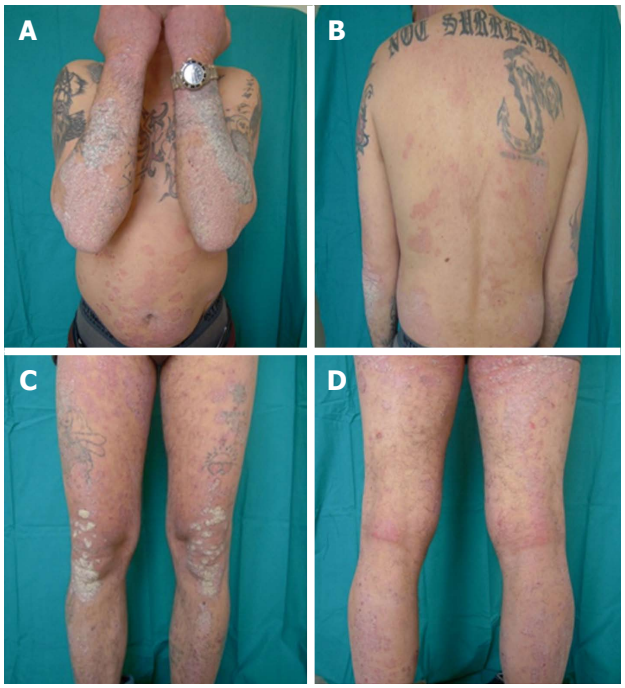

Figure 1 Basaline features: Psoriasis Area and Severity Index score 11.5, starting dose of cyclosporine 4 mg/kg per day.

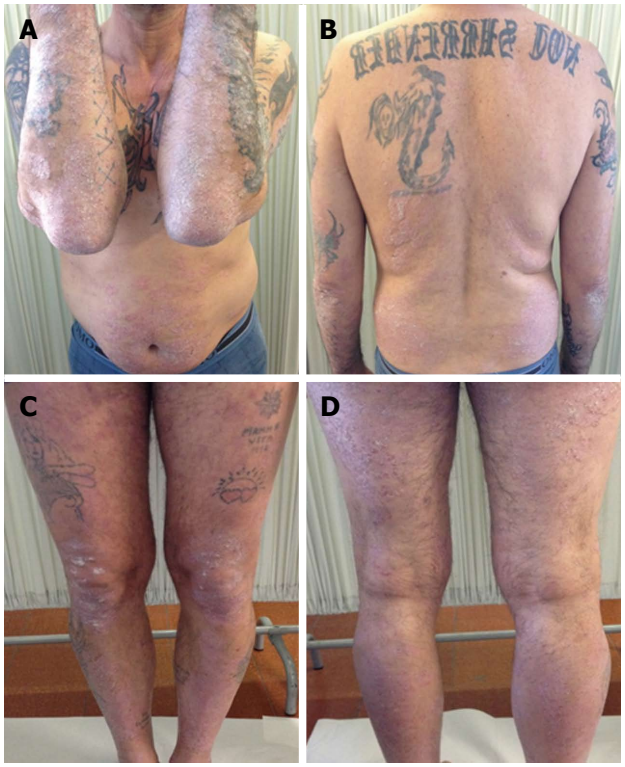

Figure 3 Treatment with etanercept: At week 12 Psoriasis Area and Severity Index score 16.2.

mo of therapy with adalimumab (Figure 5).

Nevertheless cyclosporine therapy was associated to adalimumab to achieve a reduction of the PASI score.

After 12 wk the patient showed a PASI score and DLQI improvement with further reduction of liver

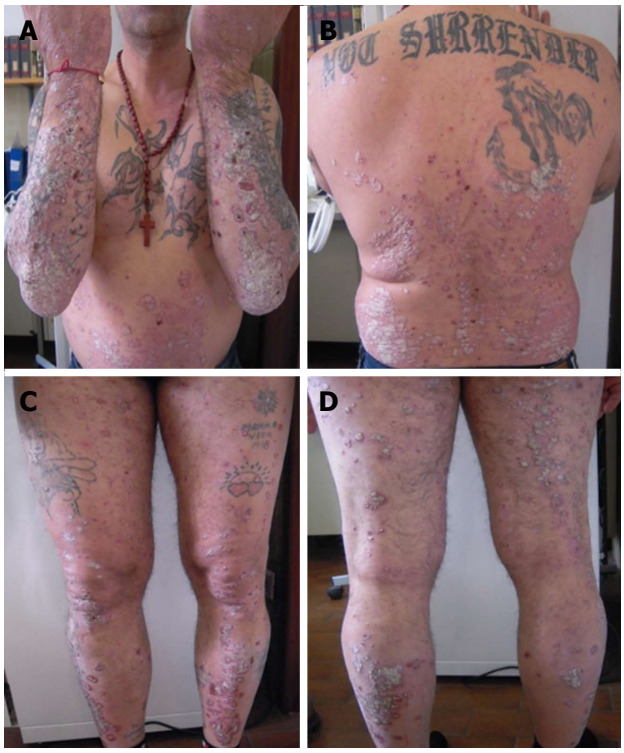

Figure 2 Week 48: Clinical worsening (Psoriasis Area and Severity Index score 22.8) after reduction cyclosporine therapy.

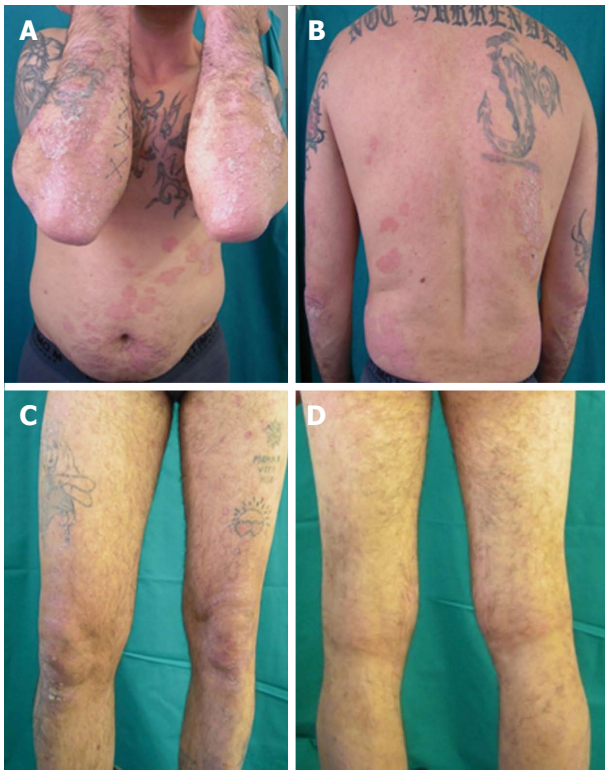

Figure 4 Treatment with infliximab: Week 16 Psoriasis Area and Severity Index score 15.

enzymes (AST: 40 U/L, ALT: 48 U/L, γ-GT: 60 U/L); liver ultrasonic imaging documented a mild steatosis and the HCV RNA status remained unaffected (Figure 6).

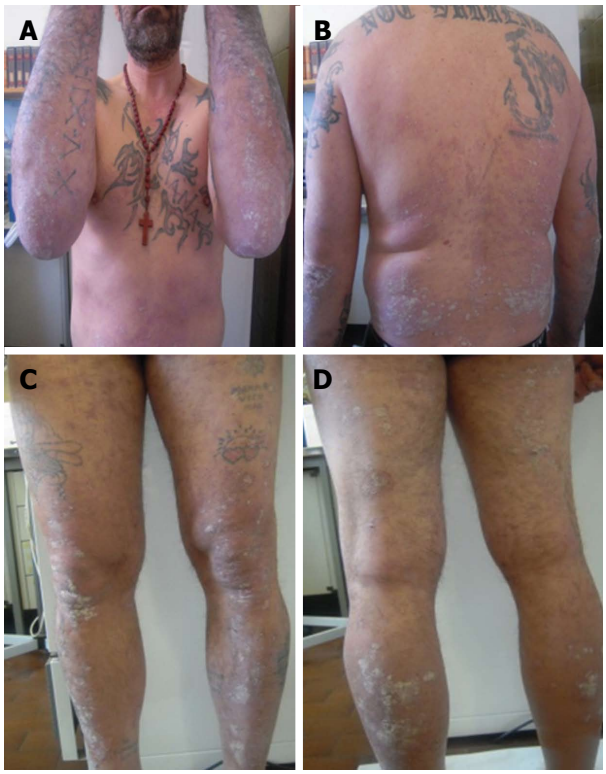

Figure 5 Treatment with adalimumab: Week 12 Psoriasis Area and Severity Index score 22.4.

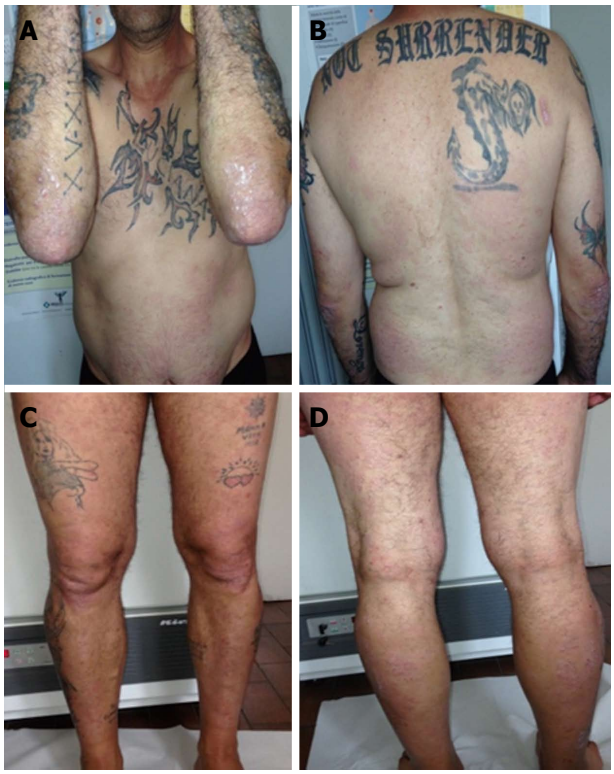

Figure 6 Combination therapy with cyclosporine and adalimumab: Week 12 Psoriasis Area and Severity Index score 2.3.

Currently, after a follow-up of 24 mo the patient performs the combined treatment with adalimumab and cyclosporine in association with clinical and instrumental investigations, showing a good clinical control of the skin lesions, as well as of the chronic HCV infection.

DISCUSSION

The present article reports our personal experience with TNF-α blockers in the handling of a patient with plaque-type psoriasis and concomitant chronic HCV infection, evaluating their efficacy and safety. Furthermore it shows that these treatments did not amplify the viral load and liver enzyme values.

Direct liver toxicity in psoriatic patients under treatment with TNF-α blockade is rare[14], although they may exacerbate the concurrent infections as well as reactivation of infections (*e.g.*, tuberculosis); however their effects on the course of HBV or HCV infections are not well estimate[15].

Thus, in patients qualified for anti TNF-α therapy, a screening for tuberculosis (chest radiography, quantiferon tb gold assay or mantoux test), HBV, human immunodeficiency virus, cytomegalovirus, herpes viruses and HCV are mandatory[16,17].

TNF-α is a cytokine involved in several inflammatory reactions and autoimmune disorders, at the same time, playing a crucial role in the pathogenesis of HCV through the mediation of apoptosis and the maintenance of inflammatory processes. TNF-α is produced by hepatocytes in patients who are chronically infected with HCV, regulating viral replication and the relative hepatocyte damage[18,19].

According to the literature, in HCV patients, serum and hepatic levels of TNF-α and TNF-α receptor (p75) are increased, showing a direct correlation with serum transaminase levels, histological activity and fibrosis, but not with serum HCV RNA levels and/or viral genotype[20-22]. Besides, it is known that over-expression of TNF-α is associated with a negative prognosis and a relative resistance to INF therapy[23].

Therefore in the context of HCV the effect of TNF-α blockade could have potential healthful role because TNF-α appears to be engaged in the pathogenesis of liver fibrosis, inducing apoptotic pathways[24].

On the contrary, it is known that TNF-α is able to recruit and activate macrophages, natural kille (NK) cells, T cells and antigen-presenting cells; so, this cytokine induces the host's immune response against infective pathogens and plays an important role in the control of viral infection. Thus, the reduction of TNF-α levels by biological drugs may increase the risk of an excessive viral replication as well as of a reactivation of chronic HCV infection[9]. However, there are not sufficient data about the assessment of the potential specific differences among the anti TNF-α drugs regarding their effect on viral replication[25].

The occurrence of autoimmune phenomena, encompassing non-organ specific autoantibody formation [including anti-double-stranded-DNA (dsDNA), rheumatoid factors and anti-cardiolipin] is a frequent event in patients treated with biologic agents[26,27]. In this regard,

Vauloup *et al*[28] showed the formation of anti-nuclear and anti-dsDNA antibodies in HCV patients treated with anti-TNF-α inhibitors. Finally, in literature, are reported also seventeen cases of TNF-α-induced hepatitis (in patients without a positive medical history of liver disease), mainly caused by infliximab and resembling to hepatitis type 1[29-33].

Data on the efficacy and safety of anti-TNF-α in psoriatic patients with concomitant chronic HCV are very limited[9,11,12,34,35].

In literature there are reports about patients showing an increasing liver function, during treatment with biologic therapies (infliximab, adalimumab and etanercept), although the simultaneous administration of other therapies render difficult the evaluation of this effect[36,37]. At the same time, studies regarding psoriatic arthritis patients affected by HCV, after a follow-up of 12 mo did not reveal any significant increase in viral load, without showing alterations of liver enzymes and, neither clinical evidence of flaring of their liver disease[10].

In addition, a retrospective analysis showed that the risk of TNF-α inhibitors (etanercept and adalimumab) related to HBV or HCV reactivation is very low in these patients[14].

In this case report, our patients, before begin the treatment showed high liver enzymes and HCV RNA serum levels. During adalimumab and cyclosporine treatment the viral load and transaminases decreased together with a clinical improvement.

Cyclosporine is a powerful immunosuppressive agent that has clinical application in the treatment of autoimmune disorders, but several studies in the literature, both *in vitro* and *in vivo*, suggests that this drug also exerts an inhibitory effect on HCV replication at standard therapeutic dose[38]. Besides, literature reports also studies about the treatment of rheumatoid arthritis (RA) or autoimmune disorders with the combination therapy of anti-TNF-α and cyclosporine in HCV patients, highlighting the efficacy and safety in controlling HCV viremia and liver toxicity[39,40]. In this regard, Giannitti *et al*[39] described that 7 RA patients with chronic HCV have been treated so far, 4 with Etanercept and 3 with adalimumab combined with cyclosporine. After 6 mo of therapy, viral load decreased of 67% of the initial value and both aminotransferases also remained within normal limits in all patients over time.

This study focuses on the safety and efficacy in the short time of anti-TNF-α therapy in a HCV patient with psoriasis. However, to date, the literature lacks of results on the use of biologic treatments in long term, in this class of patients.

Serum aminotransferase, gammaglutamyl-transferase, total bilirubin, cryoglobulins, complete blood count, creatinine, urine exam, serum anti-HCV antibodies, assessment of HCV-RNA, liver ultrasonography in addition to an evaluation of the hepatologist are recommended in patients candidate for anti TNF-α agents, in order to evaluate the liver disease stage and a possible need for antiviral therapy. In addition, liver function tests should be performed every three months during treatment with TNF-α inhibitors.

In patients with plaque-type psoriasis and concomitant chronic HCV infection the treatment with cyclosporine and anti TNF-α agents should be considered safe, efficacy and well-tolerated as well as able to decrease liver enzymes and viral load.

Large-scale studies and long follow-ups are needed to successfully evaluate the risks and benefits of TNF-α blockades in psoriatic patients with a HCV infection.

COMMENTS

Case characteristics

A 47-year-old man was diagnosed with a moderate-severe plaque-type psoriasis ever since 7 years. His medical history included familiarity for psoriasis and chronic hepatitis C infection.

Clinical diagnosis

Baseline Psoriasis Area and Severity Index score was 11.5 and Dermatology Life Quality Index was 16. Treatments with several different topical therapies for psoriasis, including corticosteroids, vitamin D derivatives (calcipotriol, calcitriol or tacalcitol) were ineffective, while joint ultrasound showed no signs of psoriatic arthropathy.

Differential diagnosis

Hepatotoxicity induced by etanercept, viral reactivation.

Laboratory diagnosis

At week 6 after the first biological treatment with etanercept, the authors detected an increase of liver enzymes with the following values: Aspartate aminotransferase: 99 U/L, alanine aminotransferase: 88 U/L and gamma glutamyl transferase: 99 U/L; while hepatitis C virus (HCV) RNA remained always stable. Once Etanercept was discontinued and adalimumab was started, liver enzymes decreased concurrently.

Imaging diagnosis

The ultrasonic imaging of the liver showed moderate hepatomegaly with sharp and diffuse dishomogenity and minimal steatosis, while joint ultrasound showed no signs of psoriatic arthropathy.

Pathological diagnosis

A cutaneous punch biopsy revealed a plaque-type psoriasis.

Treatment

Cyclosporine (4 mg/kg per day), etanercept (50 mg/wk) and adalimumab (80 mg for the induction and 40 mg for the maintenance).

Related reports

This study shows that anti-tumor necrosis factors (TNF)-α inhibitors in patients with psoriasis and HCV appear to be effective and safe in the short term, but there are still insufficient data to estimate their long term safety.

Experiences and lessons

Combination therapy with cyclosporine and anti TNF-α agents in patients with plaque-type psoriasis and concomitant chronic HCV infection should be considered safe, efficacy and well-tolerated as well as able to decrease liver enzymes and viral load.

Peer-review

This is an interesting case that deserves to be published in the journal.

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CASE REPORT

Black esophagus syndrome associated with diabetic ketoacidosis

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Informed consent statement: The patient involved in this study gave his informed written consent prior to study enrollment, authorizing the use and disclosure of his protected health information.

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Abstract

Acute esophageal necrosis, also known as "black esophagus syndrome", is a rare acute esophageal disease that is often associated with vomiting and upper gastrointestinal haemorrhage. At present, little is known regarding the pathogenesis of this disease. We present the case of a 50-year-old white male patient with diabetic ketoacidosis suffering from acute esophageal necrosis with nausea and vomiting but without any clinical signs of upper gastrointestinal bleeding.

Key words: Diabetic ketoacidosis; Acute esophageal necrosis; Black esophagus syndrome

Core tip: The aetiology and pathogenesis of the so-called black esophagus syndrome are unclear. This case report supports a possible link between the occurrence of diabetic ketoacidosis and the black esophagus syndrome.

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INTRODUCTION

Acute esophageal necrosis (AEN), also known as "black esophagus syndrome", is a rare pathological

condition typically characterized by a circumferential black-appearing esophageal mucosa, which mostly affects the distal portion of the esophagus and stops abruptly at the gastro-esophageal junction[1,2]. Although the aetiology of AEN is still unclear, it is likely to be multifactorial, arising from an ischaemic insult to the esophagus, an impaired local defence of the mucosal barrier systems and injury from backflow of gastric contents. Major complications of AEN include stenosis or stricture formation in the middle-distal esophagus, perforation, mediastinitis, and mortality. The overall mortality is approximately 30% and is largely related to the underlying medical conditions[1,2].

In this report, we present the case of an adult patient with AEN associated with diabetic ketoacidosis.

CASE REPORT

A 50-year-old white male patient with type 2 diabetes mellitus (treated with metformin 2 g/d) and hypertension (treated with doxazosine 4 mg/d) recently was admitted to the Emergency Department of our university hospital. He presented dysphagia, vomiting (without any clinical signs of acute upper gastrointestinal bleeding), polyuria, polydipsia and low-grade fever. These symptoms had started about two days earlier with epigastric/abdominal pain, nausea and vomiting. The patient strongly denied the ingestion of caustic substances or alcohol abuse. Twelve years earlier, he had undergone an exeresis of a superficial nasal melanoma.

Laboratory analyses revealed severe hyperglycemia (40 mmol/L), hyponatremia (121 mmol/L), hypokalemia (2.71 mmol/L), severe metabolic acidosis with glycosuria and ketonuria. Laboratory analyses also revealed increased serum creatinine levels, hypoalbuminemia, moderate leukocytosis and elevated plasma C-reactive protein concentrations. Upon physical examination, the patient appeared dehydrated, was hypotensive at 90/60 mmHg, tachycardic at 120 beats/min, and had a soft and non-tender abdomen. Chest X-rays and abdominal ultrasonography were normal.

The patient was admitted to our Endocrinology Division with a diagnosis of diabetic ketoacidosis (DKA). An appropriate treatment with intravenous hydration, potassium supplementation and insulin infusion was promptly started. Intravenous piperacillin/tazobactan was also administered intravenously every 8 h. After approximately 36 h of insulin infusion, the daily plasma glucose profile improved, the serum creatinine and electrolyte levels normalized, the ketoacidosis resolved, and the gastro-intestinal symptoms also improved. Thus, we shifted the patient's insulin therapy to multiple daily injections.

The patient underwent upper gastrointestinal endoscopy for persistent dysphagia, which showed a circumferential necrosis of the middle and distal portions of the esophagus (starting from 24 to 40 cm from the incisors) with an abrupt transition at the gastro-esophageal junction (Figure 1A-C). No endoscopic findings of suspected esophageal metaplasia and gastro-duodenal pathology were observed. A chest computed tomography revealed a thickened distal esophagus but excluded the presence of esophageal perforation or mediastinal infection/abscess. The patient was then treated with high-dose intravenous proton-pump inhibitors and albumin infusion and was kept initially nil-per-os (a total parenteral nutrition was maintained for approximately 15 d). Then, he was treated with a semi-liquid diet for the subsequent 5-6 d.

A second gastrointestinal endoscopy, performed approximately 1 wk after diagnosis, was essentially unchanged. Another gastrointestinal endoscopy, performed approximately 15 d after diagnosis, showed a marked reduction in the esophageal necrosis and a loss of the superficial epithelial lining (Figure 1D and E). An esophageal biopsy revealed the presence of tissue necrosis, granulated tissue and marked leukocyte infiltration with hemosiderosis.

After 4 wk, the patient was discharged from the hospital without any clinical gastro-intestinal symptoms and was prescribed lansoprazole 60 mg/d and metformin 2 g/d. Approximately three weeks after the hospital discharge, the patient underwent esophageal X-rays, owing to the appearance of dysphagia, which revealed the presence of a stenosis (with a length of about 10 cm) in the middle and distal third of the esophagus with a luminal diameter of about 1 cm. The patient underwent three consecutive sessions of esophageal endoscopic dilation with through-the-scope (TTS) balloons (maximum TTS-balloon diameter of 15 mm) over a period of three months with a complete resolution of dysphagia. An esophageal biopsy performed during the procedures was normal and excluded the presence of dysplasia and Barrett's esophagus.

DISCUSSION

AEN or black esophagus syndrome is a rare acute medical condition. Overall, fewer than 90 cases of AEN have been reported in the literature until 2007[1], making the diagnosis of this esophageal disorder very uncommon. Diagnosis of AEN is made endoscopically in an appropriate clinical setting by observing a striking diffuse circumferential black appearance of the esophageal mucosa, almost universally affecting the distal portion of the esophagus and stopping at the Z-line[1,2]. The aetiology of AEN is multifactorial, resulting from a combination of tissue hypoperfusion, massive reflux of gastric secretions, and diminished mucosal defences in the esophagus. Generally, AEN is more common in elderly male patients with multiple serious co-morbidities, and it characteristically presents with signs of upper gastrointestinal haemorrhage (occurring in up to 90% of cases). Major risk factors for AEN include male sex, older age, alcohol abuse, hypertension,

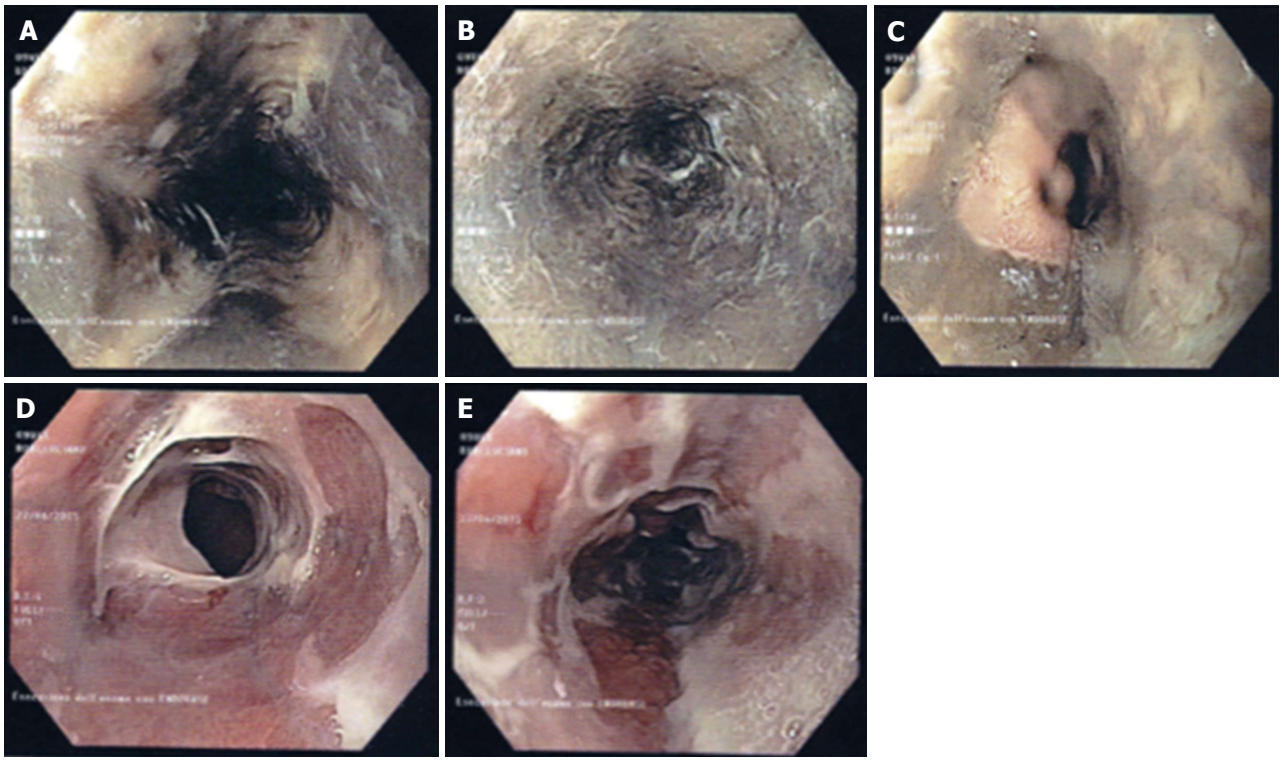

Figure 1 Upper gastrointestinal endoscopy findings. A-C: First upper gastrointestinal endoscopy: Typical endoscopic findings of AEN; D and E: Third upper gastrointestinal endoscopy: Improvement/resolution of AEN after treatment. Complete disappearance of the black mucosa with whitish membranes covering the subepithelial surface of the esophagus. AEN: Acute esophageal necrosis.

chronic kidney disease, malnourishment, and vascular diseases[1,2]. Differential diagnosis includes malignant melanoma, melanocytosis, coal dust deposition, acanthosis nigricans of the esophagus, and caustic ingestion. The overall prognosis of AEN is poor, and nearly one third of patients succumb to the underlying critical illness[1,2]. Although the therapeutic modalities are not currently standardized, the aggressive treatment of the underlying medical conditions with haemodynamic resuscitation, total parenteral nutrition and acid suppression with high-dose intravenous proton-pump inhibitors should be immediately instituted in all patients with suspected or established AEN. The most common complications of AEN are esophageal stenosis and stricture formation; these complications occur in up to 15% of patients and usually appear as early as 1 to 3 wk after the diagnosis[1,2].

In the largest multicentre series of reviewed cases of AEN, Gurvits *et al*[3] have recently found that nearly 90% of the patients are moderately hyperglycaemic. However, although some previous case reports had also shown a possible association between AEN and DKA[4,5], none of the patients included in this recent multicentre case series showed any evidence of DKA at the time of hospital admission[3].

We believe that our case report is clinically relevant because it further supports the possibility that DKA may be associated with the occurrence of AEN. Notably, our case report also shows that AEN can occur in a middle-aged male patient with DKA without any clinical signs of hematemesis, coffee ground emesis or melena and the coexistence of important co-morbidities (except for the presence of hypertension).

Thus, although to date DKA has been rarely reported as a possible cause of AEN, it is essential to diagnose AEN in patients with DKA as a potential cause of mortality or morbidity. Indeed, the early recognition and management of AEN will result in improved clinical outcomes as the medical world gets more familiar with this rarely diagnosed and important clinical syndrome.

COMMENTS

Case characteristics

A 50-year-old white man with type 2 diabetes and hypertension was admitted to the Emergency Department with dysphagia, vomiting, polyuria, polydipsia and low-grade fever.

Clinical diagnosis

The diagnosis of black esophagus syndrome, also known as acute esophageal necrosis, is made endoscopically by observing a striking diffuse circumferential black appearance of the esophageal mucosa, almost universally affecting the distal portion of the esophagus and stopping at the Z-line.

Differential diagnosis

Differential diagnosis includes malignant melanoma, melanocytosis, coal dust deposition, acanthosis nigricans of the esophagus, and caustic ingestion.

Laboratory diagnosis

Most laboratory data are normal, except for moderate leukocytosis, hypoalbuminemia and anemia (especially if upper gastrointestinal haemorrhage is also present).

Imaging diagnosis

The diagnosis of black esophagus syndrome is made endoscopically and is typically characterized by a circumferential black-appearing esophageal mucosa, which mostly affects the distal portion of the esophagus and stops abruptly at the gastro-esophageal junction.

Pathological diagnosis

Esophageal biopsy shows the presence of tissue necrosis, granulation tissue and marked leukocyte infiltration with hemosiderosis.

Treatment

Although, to date, therapeutic modalities are not standardized, the aggressive treatment of the underlying medical conditions with haemodynamic resuscitation, total parenteral nutrition and acid suppression with high-dose intravenous proton-pump inhibitors should be immediately started in all patients with suspected or established black esophagus syndrome.

Related reports

Black esophagus syndrome is a rare acute medical condition. Very few studies have reported an association between black esophagus syndrome and diabetic ketoacidosis.

Term explanation

The black esophagus syndrome is a rare pathologic condition typically characterized by circumferential black-appearing esophageal mucosa, which mostly affects the distal portion of the esophagus and stops abruptly at the gastro-esophageal junction.

Experiences and lessons

The black esophagus syndrome is an under-recognized disease and there is need of increased attention to the presence of this acute esophageal disorder.

Peer-review

This is an interesting case report of a rare esophageal acute disease.

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CASE REPORT

Herpes simplex induced necrotizing tonsillitis in an immunocompromised patient with ulcerative colitis

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Abstract

We here present the case of a 22-year-old female of Suriname ethnicity with ulcerative colitis who received treatment with mercaptopurine and infliximab. She presented herself with a severe necrotizing tonsillitis due to herpes simplex virus type-1 (HSV-1). Combination therapy consisting of immunomodulators and anti-tumor necrosis factor (TNF) agents is increasingly being used. Anti-TNF therapy is associated with an increased risk of developing serious infections, and especially patients receiving combination treatment with thiopurines are at an increased risk. We here show that HSV infections can cause a severe tonsillitis in immunocompromised patients. Early recognition is essential when there is no improvement with initial antibiotic therapy within the first 24 to 72 h. HSV infections should be in the differential diagnosis of immunocompromised patients presenting with a necrotizing tonsillitis and can be confirmed by polymerase chain reaction. Early treatment with antiviral agents should be considered especially if antibiotic treatment fails in such patients.

Key words: Herpes simplex virus; Tonsillitis; Ulcerative colitis; Immunosuppression; Anti-tumor necrosis factor agents

Core tip: Combination therapy that consists of immunomodulators and anti-tumor necrosis factor (TNF) agents is increasingly being used for patients with chronic inflammatory diseases, such as ulcerative colitis. Anti-

TNF therapy is associated with an increased risk of developing serious infections, and especially patients receiving combination treatment with thiopurines are at an increased risk. This is the first report of an acute severe tonsillitis caused by herpes simplex virus in an immunocompromised patient due combination treatment with a thiopurine and an anti-TNF agent.

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INTRODUCTION

Viral throat infections are a common problem and are generally self-limiting. Viral causes of a tonsillitis include: rhinovirus, respiratoir syncytial virus (RSV), Epstein-Barr virus (EBV), parainfluenza, influenza, Coxsackievirus, adenovirus, *etc*[1]. There are two types of the herpes simplex virus (HSV): HSV-1 and HSV-2. HSV-1 can cause primary or recurrent infections, with the most common manifestation as vesicular lesions of the oral mucosa. HSV-2 is known as genital herpes simplex. However, both HSV types can cause herpes labialis as well as genital herpes[2], which can extend into other organs, such as the hard palate, tonsils, liver, lungs and eyes. A primary HSV infection can result in an acute pharyngotonsillitis. The diagnosis of an HSV infection can usually be made based on the clinical picture. The diagnosis can be confirmed by polymerase chain reaction (PCR), which is considered as the gold standard, and with serology and/or histology.

CASE REPORT

A 22-year-old female of Suriname ethnicity with known beta thalassemia and ulcerative colitis presented herself to the family physician with a sore throat. She used infliximab, mercaptopurine, allopurinol and mesalamine enema's. Treatment with feneticillin was started (500 mg 3 times daily) under the suspicion of a bacterial tonsillitis. After 4 d, the patient presented herself to the emergency department of our hospital because of severe dysphagia for solid and liquid foods and intermittent fever up to 39.2 Celsius. An acutely ill patient was seen with a heart rate of 135 per minute and a blood pressure of 100/60 mmHg. Her neck was diffusely swollen and painful at palpation. Cervical lymphadenopathy was seen. Oral examination revealed severely enlarged tonsils that were covered with a grey-whitish exudate. No other lesions were observed and there was no trismus. Because of a symmetric pharynx arch there was no suspicion of a peritonsillar abscess at physical examination. Laboratory investigation showed an increased C-reactive protein of 137 mg/L, Hb 4.5 mmol/L, leucocyte count of 4.7 $\times$ 10^9/L (leucocyte differentiation: Neutrophils 55%, eosinophils 1%, basophils 1%, lymphocytes 38%, monocytes 4%) and a thrombocyte count of 232 $\times$ 10^9/L. Cultures of throat and nasopharyngeal swabs as well as blood cultures were negative. Viral screening using PCR and plasma viral load measurements were negative for cytomegalovirus and EBV. A multiplex PCR analysis for respiratory viruses, including rhinovirus, adenovirus, RSV, parainfluenza and influenza was also negative. The patient was admitted and amoxicillin was started instead of feneticillin because of the immunocompromised status and the fact that she did not respond to feneticillin treatment. A computed tomography (CT)-scan showed bilateral heterogeneous contrast enhancement of both enlarged pharyngeal tonsils and arytenoids. Imaging did not reveal a peritonsillar or retropharyngeal abscess. At laryngoscopy a swollen nasopharynx was seen that was covered with grey-whitish exudate, and ulcerations of both arytenoids and in the aryepiglottic fold (see record). The patient deteriorated and became respiratory insufficient. Empirical treatment with valacyclovir was started (1000 mg 3 times daily) under the suspicion of an HSV infection. Treatment with mercaptopurine and allopurinol was stopped. The patient responded to the antiviral treatment within one day. The diagnosis of HSV type Ⅰ was confirmed by PCR of the nose and throat swabs and by serology. The patient was seen at the outpatient clinic 10 d after discharge and was asymptomatic.

DISCUSSION

HSV can cause life-threatening infections in immunocompromised patients[3-5]. We here describe a patient with ulcerative colitis who received treatment with infliximab and mercaptopurine. Therapeutic efficacy of combination therapy with anti-tumor necrosis factor (TNF) agents (such as infliximab) and immunomodulators (including mercaptopurine) should be balanced against the potential risks, such as infections[6]. The use of anti-TNF therapy has been associated with serious infections and especially patients receiving combination treatment with thiopurines seem to be at an increased risk[4,7-9]. Our patient developed a severe necrotizing tonsillitis due to an infection with HSV, which was confirmed by PCR and serology. She responded promptly to antiviral treatment which was empirically started after failure of antibiotic therapy. Mercaptopurine treatment was stopped and infliximab was continued. Histological findings were reported by Wat *et al*[10] who described a patient with a herpes simplex infection that also caused an acute necrotizing tonsillitis. In contrast to our patient, this particular patient had a blanc medical history and was not immunocompromised. We here demonstrate that histology is not always required in order to accurately diagnose herpes simplex induced necrotizing tonsillitis.

To the best of our knowledge, this is the first report of an acute pharyngotonsillitis caused by HSV in an immunocompromised patient due combination

treatment with a thiopurine and an anti-TNF agent. Hence, HSV infections should be in the differential diagnosis when immunocompromised patients present with a severe necrotizing tonsillitis, and early treatment with antiviral agents should be considered especially if antibiotic treatment fails.

COMMENTS

Case characteristics

A 22-year-old female with known ulcerative colitis presented herself to the family physician with a sore throat.

Clinical diagnosis

Herpes simplex induced necrotizing tonsillitis in an immunocompromised patient.

Laboratory diagnosis

C-reactive protein of 137 mg/L, Hb 4.5 mmol/L, leucocyte count of 4.7 × 10^9/L (leucocyte differentiation: Neutrophils 55%, eosinophils 1%, basophils 1%, lymphocytes 38%, monocytes 4%).

Imaging diagnosis

A computed tomography-scan showed bilateral heterogeneous contrast enhancement of both enlarged pharyngeal tonsils and arytenoids. At laryngoscopy a swollen nasopharynx was seen that was covered with grey-whitish exudate, and ulcerations of both arytenoids and in the aryepiglottic fold.

Treatment

Valacyclovir (1000 mg 3 times daily).

Experiences and lessons

Herpes simplex virus infections should be in the differential diagnosis when immunocompromised patients present with a severe necrotizing tonsillitis, and early treatment with antiviral agents should be considered especially if antibiotic treatment fails.

Peer-review

An highly interesting case report.

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