second-line kinase inhibitor against chronic myelogenous leukemia. Preclinical and clinical studies have been conducted for lung cancer,[46] urothelial cancer,[47] and ovarian cancer.[48] A few researchers have considered SRC as a target for gastric cancer therapy.[41] As our data showed, SRC amplification is more prevalent in node-positive and more advanced cases; thus, SRC amplification is likely to be an important clinical determinant of the outcomes of gastric cancer patients.

STK15 is known as Aurora kinase A and has also been considered as a target of many cancers including the brain,[49] esophagus,[50] larynx,[51] and colon,[52] but the use of STK15 as a therapeutic target of gastric cancer has not been reported. Several targeting drugs against Aurora A kinase are presently available including VX-680;[53,54] thus, some patients with STK15 amplification may benefit from these drugs.

Since we adopted a tissue microarray (TMA) approach, the results here cannot escape the problems of sampling biases, especially when heterogeneous genetic change is considered.[55] Our core sizes taken are larger than ordinary ones (0.6, 1.0 and 2.0 mm) that the most popular tissue microarrayer generates, but we were aware that we missed some genetic information in heterogeneous cancer tissue. We are currently duplicating these samples, that is two and more cores are taken from the same block, and the trend is basically same (data not shown).

In conclusion, our study suggests the following: (i) a FISH analysis of 10 kinases is feasible as a routine diagnostic measure; (ii) the co-amplification status of kinases may further help to modify therapeutic strategies, especially when dual inhibitors or pan-inhibitors of kinases are included in the treatment regimen; (iii) the amplifications of kinases occur in a stochastic manner, that is, there is no 'amplification phenotype' analogous to a 'mutator phenotype'; and (iv) some kinase amplifications start at an early disease stage, while others are correlated with metastasis and progression.

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Review Article Open Access

Assessment Scales for Nicotine Addiction

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Abstract

The genetics of nicotine addiction has been probed using combinations of genetic markers and questionnaire results regarding individual smoking behavior. Recently, the association of nicotine addiction with various candidate gene or gene polymorphisms has been proposed based on genome-wide association studies and candidate gene approaches, but the assessment of smoking behaviors including how severely each smoker is addicted, is typically performed using limited measures such as questionnaires. In this review, we present part of our recent data in which different scaling methods detected different genetic polymorphisms associated with different aspects of addicted smoking behaviors, as determined using questionnaire responses and genotyping data for 2500 Japanese elderly subjects. Several scaling methods have been developed to estimate nicotine addiction; here, we briefly review four scaling methods in addition to the Fagerström Tolerance Questionnaire (FTQ) and the Fagerström Test for Nicotine Dependence (FTND): The Tobacco Dependence Screener (TDS), the Wisconsin Inventory of Smoking Dependence Motives (WISDM), the Cigarette Dependence Scale (CDS), and the Nicotine Dependence Syndrome Scale (NDSS). The characteristics and powers of these scales are also discussed. These scales are used regionally; for example, the TDS is mainly used in Japan, while the NDSS and the WISDM are used in the US. Taking advantage of the characteristics of these scaling methods and comparing them with each other in various populations may be useful for elucidating the genetic and non-genetic nature of nicotine dependence.

Keywords: Nicotine addiction; Nicotine dependence

Abbreviations: FTQ: Fagerström Tolerance Questionnaire; FTND: Fagerström Test for Nicotine Dependence; TDS: Tobacco Dependence Screener; WISDM: Wisconsin Inventory of Smoking Dependence Motives; CDS: Cigarette Dependence Scale; NDSS: Nicotine Dependence Syndrome Scale

Introduction

Cigarette smoking is still a major cause of many preventable diseases [1]. The pharmacologic effect of nicotine plays a crucial role in tobacco addiction [1,2]. When issues around tobacco use are considered, "nicotine addiction" can be regarded as a roadblock that needs to be overcome. The importance of nicotine in maintaining smoking and in cessation difficulty has been well acknowledged [3]. Numerous twin studies have investigated the contributions of genetic and environmental factors to nicotine addiction [4-6]. Recent advances made through the use of linkage and association approaches, especially genome-wide association (GWA) studies, have identified susceptibility genes for addiction including nicotine addiction [7].

Along with the progress of research regarding nicotine addiction, the measurement of nicotine addiction has been recognized as an important issue. Progress in tobacco research may depend on improved measurement [8]. How nicotine addiction is defined and measured may influence the results and interpretations of research or clinical outcomes.

From a historical perspective, the Fagerström Tolerance Questionnaire (FTQ) [9] and its shorter version, the Fagerström Test for Nicotine Dependence (FTND) [10], are the most notable scales and have been used in both clinical and research settings [7]. However, the Fagerström scales were intended as measures of physical tolerance per se [9]; therefore, they do not assess several important aspects of nicotine dependence, such as cravings, subjective compulsion to smoke, nicotine withdrawal, behavioral saliency, or behavioral automaticity, which are often regarded as core constructs for dependence [11].

Nicotine addiction can also be assessed using diagnostic criteria based on the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association [12,13] and the International Classification of Disease 10th revision (ICD-10) from the World Health Organization (WHO) [14]. The Tobacco Dependence Screener (TDS, reviewed later) [15] is a 10-item questionnaire for screening tobacco/nicotine dependence according to these criteria.

We previously reported the association between neuropeptide Y receptor 2 (*NPY2R*) polymorphism and smoking behavior of elderly Japanese [16], in which both the FTND and the TDS were used as assessment scales for nicotine addiction. Analyses of information about smoking behavior and genotyping data of rs4425326 and rs6857715 from about 2500 subjects including various smoking status revealed that male but not female ever-smokers (current and ex-smokers) having the rs4425326 TT genotype had significantly higher FTND scores (P= .003) and greater CPD (cigarettes smoked per day) than those with other genotypes. No association was found between the TDS and these polymorphisms. We also conducted association study between smoking behavior and the Neurexin 1 (*NRXN1*) gene polymorphisms, rs2193225 and rs6721498 using the same subjects [17]. In contrast, we have found that male ever-smokers with the rs2193225 GG type were more prevalent in the higher TDS score category (P= .056), but not in the higher FTND score category. These observations indicate that the traits detected by the scores of the two questionnaires are supposedly different, and how the genetic components control these traits in establishing individual nicotine dependence has not been elucidated.

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Some assessment scales have been developed with the goal of capturing diverse aspects of nicotine dependence. These scaling methods are being improved in each successive version. In the present article, we briefly review four relatively new scales and discuss their characteristics and powers (Table 1).

Assessment scales	Number and gender of subjects	Race of subject	Age of subjects, years old	Reliability (Internal consistency), α	Indexes correlated with the scale	References associated with the scale
TDS [15]	Sample1: 58 males	Japanese	27.6 (±11.1)[a]	.81	Years of smoking, CPD	Studies on varenicline treatment [19,20] Studies developing new tools for assessing nicotine dependence [21,22]
	Sample2: 115 males		43.1 (±15.6)[a]	.76	Years of smoking, CPD, CO levels	
	: 33 females		33.0 (±12.4)[a]	.77	None	
	Sample3: 194 males		NM	.77	Age, Years of smoking CPD	
WISDM-68 [22]	303 males, 454 females, 18 not identified	638 White 83 African-American 54 others	≥18	Total WISDM-68: .98- .99 Subscales: .84- .96	Total WISDM-68: TDS, CO, CPD, Some subscales: End of treatment relapse	Replication study [26,27] Studies on PDM and SDM [28-30] Brief WISDM [31]
CDS-12, CDS-5 [33]	Preliminary survey: mail 384, internet 145 (Gender: NM)	NM	18-70	CDS-12: .90 CDS-5: .84	Cotinine, CPD, Urge to smoke, Switching from daily to occasional smoking	Replication studies on predictivity [34,35]
	Main survey: 3009 47% males		32 (range 12-74)			
NDSS [24]	Study 1: 317 57% females	NM	44.2 (±10.3)[a]	30-item version, NDSS-T: .84 Factors: .55- .76	30-item version: CPD, Difficulty abstaining, Past severity of withdrawal	Studies comparing some scales [26,38]
	Study 2 : 802 57% females	66% White 31% Black 3% others	39.2 (±10.6)[a]			
	Study 3: 91 59% males	81% White	34.5 (±9.0) [a] (range 20-55)			

Abbreviation: TDS= Tobacco Dependence Screener, WISDM= Wisconsin Inventory of Smoking Dependence Motives, CDS= Cigarette Dependence Scale, NDSS= Nicotine Dependence Syndrome Scale, NM= Not mentioned, NDSS-T=Total NDSS, CPD= Cigarettes smoked per day, CO= Carbon monoxide, PDM= primary dependence motives, SDM= secondary dependence motives

a. Mean (± standard deviation)

Table1: Summary of assessment scales for nicotine addiction.

Assessment Scales

Tobacco Dependence Screener (TDS): The Tobacco Dependence Screener (TDS) [15] is a 10-item questionnaire for screening tobacco/nicotine dependence according to the International Classification of Diseases 10th revision (ICD-10) [14], the Diagnostic and Statistical Manual of Mental Disorders third edition revised [12] and fourth edition [13] (DSM-III-R and DSM-IV).

The questions were derived from the tobacco use section of the World Health Organization's Composite International Diagnostic Interview (WHO-CIDI), version 1.1 [18], which was designed to assess 11 dependence symptoms of ICD-10 tobacco dependence, and the DSM-III-R. The questions in a later version of the CIDI are also adapted to the DSM-IV. After combining the second and third symptoms, the TDS was developed based on these 10 symptoms. The symptoms were as follows: (1) smoking more than he/she intended, (2) a desire to quit smoking and unsuccessful efforts to quit smoking, (3) craving for tobacco, (4) withdrawal symptoms, (5) smoking to avoid withdrawal symptoms, (6) smoking despite a serious illness, (7) smoking despite health problems, (8) smoking despite mental problems, (9) feeling dependent on tobacco, and (10) giving up important activities for smoking. For each question regarding each symptom, a dichotomous response category ("yes" or "no") was possible. The number of "yes" responses was counted as the scale score.

Three samples of Japanese smokers (n=400, in total) were used to assess the reliability and validity of this scale. The Cronbach alpha coefficients of internal reliability for the TDS were .76 or greater for all the samples. The TDS was found to have a better screening performance than the Fagerström Tolerance Questionnaire (FTQ) for any of the three diagnostic criteria (ICD-10, DSM-III-R, and DSM-IV) based on Receiver Operating Characteristic (ROC) analyses.

The TDS score was significantly and positively correlated with the number of cigarettes smoked per day, the years of smoking, the severity of the three diagnoses and breath carbon monoxide levels. Additionally, the TDS score was significantly lower among those who had quit smoking, compared with those who had not.

This simplified scale showed an acceptable reliability, construct and predictive validity, and screening performance based on psychiatric diagnosis criteria.

In 2006, the Japanese National Health Insurance program began to cover smoking cessation treatment for patients who met the criteria for nicotine dependence; one of these criteria was a score of 5 or greater on the TDS. Therefore, the TDS is widely used in Japanese clinical settings. In some research on varenicline treatment, the TDS has also been used as a measure for assessing nicotine dependence [19,20].

The TDS has also been used as a smoking index in studies developing

new tools for assessing nicotine dependence [21,22]. A lower TDS score among subjects who quit smoking, compared with those who did not, has been replicated in a study reporting the predictability of the FTQ and the TDS among inpatients with coronary heart attacks [23].

The TDS is assumed to be a reliable, concise, and useful measure based on the DSM and ICD-10 assessments per se. However, the DSM assessment of dependence has been pointed out to be a dichotomous diagnostic decision conveniently classifying people as "dependent" or "not dependent" [7,24], despite its underlying multidimensionality [25]. Dichotomous measures are useful for case-finding and epidemiological studies, but may present difficulties in some research settings when the nature of nicotine dependence is considered.

Wisconsin inventory of smoking dependence motives (WISDM-68): The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68) is a multidimensional measure of dependence based on theoretically grounded motives for drug use [22]. The measure has 68 items consisting of 13 domains that identify separate motives for tobacco use. The number of items related to each motive ranges from 4 to 7. Each item is answered using a 7-point Likert scale ranging from 1 - "Not true of me at all" to 7 - "Extremely true of me". The authors attempted to define and measure dependence based on 'motivations', which were intended to illuminate mechanisms underlying the compulsive use of tobacco/nicotine using a large sample of 775 smokers.

The 13 domains (subscales) are listed below:

1. Affiliative Attachment
2. Automaticity
3. Behavioral Choice/Melioration/Alternative Reinforcement
4. Cognitive Enhancement
5. Craving
6. Cue Exposure/Associative Processes
7. Loss of Control
8. Negative Reinforcement
9. Positive Reinforcement
10. Social and Environmental Goads
11. Taste and Sensory Properties
12. Tolerance
13. Weight Control

The internal consistency coefficient of each subscale was greater than .90, with the exception of the Cue Exposure/Associative Processes subscale, for which the reliability coefficient was .88. The WISDM-68 subscales had fair-to-excellent internal consistencies (range = .73 - .95) for all six of the groups examined: men, women, daily, non-daily, white, and non-white smokers. This result means that the WISDM-68 subscales are appropriate for various populations.

Confirmatory factor analysis models were used to examine the hypothesis that the WISDM-68 is multidimensional. The results indicated that dependence measured by the WISDM-68 was not a unitary factor, but a diverse collection of distinct motives for drug use. However, strong inter-correlations among some of the subscales were seen, which does not mean that the 13-factor model was the best-fitting model possible.

Concerning measurement validation, concurrent validity and preliminary predictive validity were investigated. For concurrent validity, three indices were assessed: heaviness of smoking measured via self-report of smoking rate and via alveolar carbon monoxide (CO) levels, and the DSM-IV criteria for tobacco dependence as assessed using the Tobacco Dependence Screener (TDS). All the subscales were correlated with smoking heaviness (cigarettes per day r= .23- .76; CO r= .15- .70) and the TDS (r= .31-73). The total WISDM-68 was also correlated with the smoking indices (cigarettes per day r= .63; CO r= .55; TDS r= .72). Regression analyses revealed that the Tolerance subscale best predicted the CO level, but the Craving, Cue Exposure/Associative Processes, and Tolerance subscales were the best predictors of DSM-IV dependence.

Hierarchical logistic regression using data from a cessation study (N=238) indicated that Automaticity, Cognitive Enhancement, Negative Reinforcement and Social/Environmental Goads predicted relapse, but the total WISDM-68 score did not significantly predict relapse.

The internal consistency and validity of this scale were replicated by the group of investigators and by another one [26,27]. Interestingly, in a later study, the group of investigators has suggested that just four subscales (automaticity, craving, loss of control, and tolerance) had represented the core features of dependence [28-30]. These subscales were dubbed the "primary dependence motives (PDM)" and the remaining scales were labeled as the "secondary dependence motives (SDM)". The findings suggest that the PDM captures the more fundamental dependence-related variance and that the PDM score may reflect the emergence of clinical features especially characteristic of advanced or problematic tobacco use [30].

This measurement was followed by the Brief Wisconsin Inventory of Smoking Dependence Motives (Brief WISDM) [31]. Research using data from three independent samples aimed to shorten the WISDM by selecting subscales and reducing the sets of items. Thirty-one items were dropped, and the Behavioral Choice-Melioration subscale was dropped from the WISDM; the Negative and Positive Reinforcement subscales were then consolidated. The new WISDM short-form, comprised of 37 items and 11 subscales, was found to have a comparable internal consistency, long-term stability, concurrent validity, predictive validity and model fit with the original WISDM. The 37-item Brief WISDM is useful when the assessment burden is a consideration.

The psychometric properties and construct validity of these full and brief versions of the Wisconsin Inventory of Smoking Dependence were assessed using an internet-based sample of treatment-seeking Hungarian smokers [32]. The WISDM-37 had sufficient psychometric properties and good construct validity, compared with the WISDM-68.

In conclusion, the WISDM scales showed appropriate psychometric characteristics for the measurement of a wide variety of smoking motives and were related to some indices with regard to nicotine dependence or smoking behavior. However, most of the studies using the WISDM scales were conducted in the US or in Caucasian populations. For further confirmation of the reliability and validity, attempts to use these scales among various populations are needed.

Cigarette dependence scale – 12 (CDS-12), cigarette dependence scale – 5 (CDS-5): The Cigarette Dependence Scale [33] was developed by asking smokers via mail and through a web site to assess signs indicating a dependence on cigarettes. There are two types of scale, the CDS-12 and the CDS-5, each of which is rated using a 5 point scale. The CDS-12 is a 12-item instrument covering the main components of the DSM-IV and ICD-10 and some of the FTND. The CDS-5 is a 5-item version of the CDS-12. These items were designed to index the

dependence outcomes, such as "Please rate your addiction to cigarettes on a scale of 0 to 100" and "On average, how many cigarettes do you smoke per day?"

Internal consistency was assessed using internal consistency coefficients (Cronbach α). The internal consistency coefficients were .90(α) for CDS-12 and .84(α) for CDS-5. These coefficients were larger than the recommended level (.70). Furthermore, they were higher than that of the FTND (α= .66). Thus, a high internal consistency for both the CDS-12 and the CDS-5 was demonstrated.

To assess reliability, the intraclass coefficient correlation (ICC) for each item and scale was tested at baseline and at 15-31 days after the baseline survey. The ICC for all the items was .60 or higher, and the ICC for CDS-12 and CDS-5 was .83 or higher. The ICC for CDS-12 and CDS-5 was significantly higher than that of the FTND ($P < .001$).

The construct validity was tested to assess the "dependence in daily smokers and occasional smokers", "a 0-100 rating of the strength of the urge to smoke during the last attempt to quit", "the number of cigarette smoked per day", etc. Higher scores for the dependence items and scales were obtained for the daily smokers than for the occasional smokers. All the items and scales had a strong association with the 0-100 rating of the strength of the urge to smoke during the last attempt to quit.

A recent study [34] reported that CDS-12 predicted smoking cessation after 8 days and 6 weeks. They assessed the dependence rating, withdrawal intensity, and self-efficacy rating. The higher CDS-12 score at baseline predicted smoking abstinence after 6 days and 8 weeks, although the CDS-5 and FTND did not predict smoking cessation. A higher CDS-12 also predicted a higher withdrawal rating and a lower self-efficacy rating after 8 days, but the FTND did not yield similar predictions. These results suggest that the CDS-12 has a predictive validity. In a more recent study, the predictive validity of five cigarette dependence questionnaires (CDS-12, CDS-5, FTND, Heaviness of Smoking Index, and the Nicotine Dependence Syndrome Scale, reviewed later) was investigated. The results of this study indicated that the CDS-12 was the best predictor (OR: 3.98 per SD unit) of smoking abstinence at an 8-day follow-up [35].

In addition, the cotinine level was measured in saliva from volunteers. All the items and scales were associated with the level of cotinine. The CDS-5 was more strongly associated with the cotinine level ($R^2 = 0.21$) than the CDS-12 ($R^2 = 0.17$). The association between the CDS-5 and the cotinine level was equivalent to the association of the FTND with the cotinine level. However, the CDS-12 was less strongly associated with the cotinine level.

In conclusion, the recently developed CDS is considered to reflect the DSM-IV and the ICD-10 and FTND. The CDS has a high reliability, but its predictive validity was only recently demonstrated. This scale is expected to be used in current clinical practice because of its high reliability and validity.

Nicotine dependence syndrome scale (NDSS): The Nicotine Dependence Syndrome Scale (NDSS) [24] is a multidimensional questionnaire based on Edwards's syndromal conceptualization of dependence [36,37]. After three successive studies, a 19-item self-report scale consisting of five factors was developed using mainly participants in smoking cessation studies.

The essential elements of syndrome that Edwards proposed, which were the theoretical foundation of this scale, were as follows: a narrowing in the repertoire of drug use behavior, an increased salience of drug-seeking behavior, an increased tolerance to the drug, repeated withdrawal symptoms, repeated relief or avoidance of withdrawal symptoms by further drug use, subjective awareness of a compulsion to use the drug, and rapid reinforcement of the syndrome after relapse. Starting with these concepts applied to nicotine dependence, a 23- item questionnaire was first developed. After psychometric analysis, seven items were added in the next step, and the psychometric properties were also investigated. Finally, a factor analysis extracted five factors: drive (craving and withdrawal, and subjective compulsion to smoke), priority (preference for smoking over other reinforcers), tolerance (reduced sensitivity to the effects of smoking), continuity (regularity of smoking rate), and stereotypy (invariance of smoking), leading to a 19-item questionnaire.

The internal consistency of the omnibus summary score, the NDSS-T (for total) showed good values for both the first 23-item version and the second 30-item version (α= .86, and .84, respectively). Each factor also indicated relatively acceptable reliability coefficients for both version (.55- .83) with the exception of stereotypy in the 23-item version (α= .49), which was improved in the 30-item revision (α=.70). The test-retest reliability for the NDSS-T and each factor using the 30-item version showed an adequate level (.71- .83).

Concerning the validation analysis, more data was obtained from the first 23-item version than from the 30-item version. The NDSS-T and factor scores showed strong associations with dependent-relevant measures such as cigarettes smoked per day (CPD), difficulty abstaining, and past severity of withdrawal on both the 23-item and the 30-item version. The 23-item NDSS-T and certain factor scores were correlated with some scales reflecting smoking motives or occasions. They also predicted subsequent real-world experience such as urges when smoking, withdrawal symptoms (e.g. urge, restlessness) in acute abstinence, and outcome of cessation. These relations were maintained even when the FTQ scores were controlled and similar results were observed when the CPD was controlled. This finding supports the idea that the NDSS has an incremental utility and validity.

The results of a simultaneous regression analysis in the 30-item version showed an incremental utility of multiple scales. For smoking rate (CPD) and difficulty abstaining, all five subscales indicated independent predictive utility, while for severity of withdrawal, all the subscales except continuity showed independent utility.

Differences in the dependence measures between two ethnicities (White and African American) were examined. The NDSS-T did not show a significant difference, but the FTQ did, and significant ethnic group differences were seen in the subscales (e.g. African American showed significant lower scores for drive and continuity but higher scores for stereotypy).

In conclusion, the NDSS showed evidence of being a valid measure of dependence, though the reliability of some subscale was relatively low. The NDSS samples the multidimensional components of dependence and represents a broad conceptual framework for nicotine dependence. Several improvements are possible and needed; for example, scale revisions especially for stereotypy and continuity, incorporating FTQ scales content into the NDSS, assessing the relationship between the NDSS and DSM-based measures.

Conclusions

We have briefly reviewed the relatively new scales that are being used to assess nicotine addiction. In an effort to expand the breadth of the theories and mechanisms underlying nicotine addiction, multidimensional scales have been developed. The references which report the process of developing these measures also support that

nicotine dependence is a heterogeneous construct. Continuous efforts to capture different aspects of nicotine dependence are needed.

These scales are used regionally; therefore, taking advantage of the characteristics of these scaling methods and comparing them among various populations may be important for elucidating the genetic and non-genetic nature of nicotine dependence.

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problem solving. Predictably, this strategy provides distinct findings in different populations, highlighting the need of individualized medicine. Thus, the statement "significant controversy regarding ICS still exists" should read that there is no real controversy. Inhaled corticosteroids can be effective in suppressing bronchial inflammation with associated reduction of decline in lung function in particular subgroups of COPD (5). Therefore, it is not surprising that inflammatory phenotype-driven therapy has been extremely successful in COPD (6); that is, targeting treatment on one specific phenotype (eosinophilia) can improve disease outcome above guideline-based treatment, with effect sizes exceeding those by any novel drug in this disease. This has and can only become apparent by examining consistency of treatment effects along multiscale abnormalities of the disease.

Accordingly, the "current controversies" are the best fuel for existing perspectives in COPD. Subgroups of patients with unexpected phenotypes (e.g., those with eosinophilia [6], *see above*) have been captured as being responsive to available therapy. It is our task to give them the current perspective they deserve.

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Reply

From the Authors:

We thank Drs. Postma and Sterk for their interest in our article (1). We really do not have anything to argue against their views since some of us (Drs. Sterk and Agustí) have recently coauthored an article exactly along these lines (2). We entirely concur on the importance of understanding the complexity of chronic obstructive pulmonary disease (3) and that systems biomedicine offers a very interesting research strategy to this end (4). We hope that other investigators in the field share this view, so more effective therapeutic alternatives can be offered to specific groups (phenotypes) of patients with chronic obstructive pulmonary disease.

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Endobronchial Metastasis from Gastrinoma of the Pancreas

To the Editor:

Gastrinoma is a functional endocrine tumor of the digestive tract and pancreas that is known to cause Zollinger-Ellison syndrome. The main metastatic sites are regional lymph nodes, liver, and bones, and the lungs may also be involved (1). Here we describe a rare case of endobronchial metastasis from gastrinoma of the pancreas.

A 73-year-old male was referred to our hospital for detailed examination of prolonged cough. He had suffered from recurrent peptic ulcer during his fourth decade and was diagnosed as having pancreatic gastrinoma with liver metastasis. He had been carefully observed, receiving chronic proton pump inhibitor therapy, and had undergone resection of the right lobe of the liver to reduce the tumor mass 6 years previously, with postoperative chemotherapy of gemcitabine and uracil-tegafur. The maximal serum gastrin level was 4,300 pg/ml. He had never smoked. Computed tomography scan of the chest showed a nodule, 2.0 cm × 2.0 cm in size, in the right lower lobe and multiple micronodules in both lungs (Figure 1A). Bronchoscopic examination revealed total occlusion of the right basal bronchus by a polypoid mass (Figure 1B). A biopsy specimen from the endobronchial tumor showed the findings of neuroendocrine carcinoma (Figure 1C), immunohistochemically positive for gastrin (Figure 1D). The patient was diagnosed as having endobronchial metastasis from gastrinoma. The patient's cough disappeared with antitussive agents.

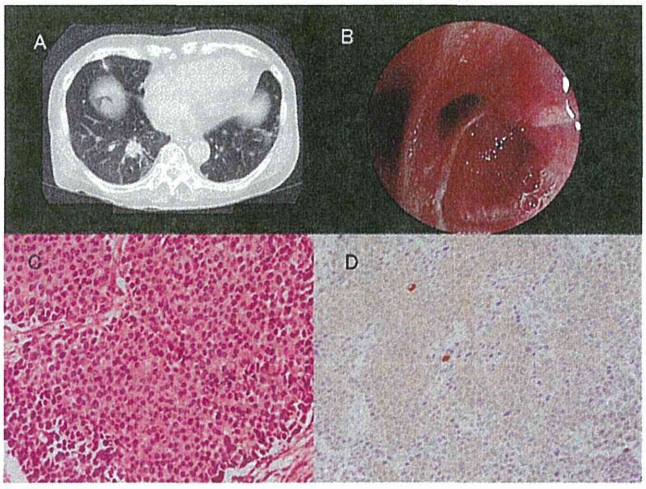

Figure 1. (*A*) Computed tomography of the chest shows a nodule, 2.0 cm × 2.0 cm in size, in the right lower lobe and multiple micronodules in both lungs. (*B*) Bronchoscopic findings show total obstruction of the right basal bronchus by a polypoid tumor. (*C*) Biopsy specimen from the endobronchial tumor shows findings of neuroendocrine carcinoma (hematoxylin and eosin staining, ×200). (*D*) Immunohistochemical staining for gastrin is positive.

Endobronchial metastasis is defined as nonpulmonary neoplasms that metastasize to the proximal central or subsegmental bronchus, in a bronchoscopically visible range, and is frequently associated with primary tumors of the kidney, colon/rectum, breast, and others (2). To the best of our knowledge, there have been no previous reports of endobronchial metastasis from gastrinoma. This is the first reported case of endobronchial metastasis from gastrinoma. Therefore, the present case reminds physicians to consider endobronchial metastasis from extrathoracic endocrine neoplasms.

Therapy for gastrinoma includes surgery for localized disease, debulking surgery for metastatic disease, and chemotherapy. More than sixty percent of gastrinomas are malignant; 5-year survival for patients with gastrinoma with liver metastases is between 40% and 75%, and it is almost 100% when no liver metastases are present (3). In this patient, tumor progression has been slow, and he remains almost asymptomatic after debulking surgery for liver metastases and chemotherapy.

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Influence of Body Mass Index on Effects of a Shared Asthma Treatment Decision-Making Intervention

Asthma is a significant public health problem, with approximately 24.6 million Americans reporting current asthma in 2009 (1). Obesity prevalence has continuously increased over the last 30 years, reaching 33.8% among U.S. adults in 2007–2008 (2). A meta-analysis of prospective studies showed a dose-dependent relationship between increasing body mass index (BMI) and the risk of incident asthma (3). Understanding the influence of BMI and obesity on effectiveness of interventions to improve asthma control will help clinicians better care for obese patients with asthma.

The Better Outcomes of Asthma Treatment study, a randomized controlled trial in 612 adults with poorly controlled asthma, found that a shared treatment decision-making (SDM) intervention improved controller medication adherence and clinical outcomes (4). Given the increased attention to the links between obesity and asthma, we conducted *post hoc* analyses to investigate whether baseline BMI modified the SDM intervention effects on asthma medication acquisition outcomes (fill/refill adherence and regimen strength) and clinical outcomes in the follow-up year. We hypothesized that obese patients would have benefitted less from the SDM intervention than did overweight or normal weight patients. Some of the results reported here were previously reported in the form of an abstract (5).

Standard BMI categories were defined: normal (18.5–24.9 kg/m^2, n = 132) and underweight (<18.5 kg/m^2, n = 7) combined, overweight (25–29.9 kg/m^2, n = 185), and obese (≥30 kg/m^2, n = 286). Using comprehensive pharmacy dispensing records, we computed continuous medication acquisition (CMA) indices (6–8) to measure fill/refill adherence for controller medications (inhaled corticosteroids, leukotriene modifiers, and others) and for long-acting β agonists (LABA) during the 12 months before and after randomization of individual participants. Controller and LABA medication regimen strength was measured by cumulative beclomethasone canister-equivalents (C-E) and salmeterol diskus-equivalents (D-E), respectively, using a standardized weighting methodology (9). Clinical

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