INTRODUCTION

Small cell carcinoma (SCC) is a high grade epithelial cancer of neuroendocrine origin, which is considered to be a distinct clinico-pathological entity. It has been reported in the literature by using various terminologies including oat cell carcinoma, anaplastic carcinoma, small cell undifferentiated carcinoma, undifferentiated carcinoma, microcytoma, reserve cell carcinoma, small cell neuroendocrine carcinoma, Kulchitsky cell carcinoma, and carcinoma with amine-precursor uptake and decarboxylase (APUD) cell differentiation. Small cell carcinoma is, however, the recommended pathological term (Beasley et al., 2005). It is most commonly of bronchogenic origin and accounts for about 20–25% of all pulmonary malignancies (Hoffman et al., 2006). Small cell carcinoma of lung is well recognized for its aggressive clinical behavior and an increased propensity for early metastases. Uncommonly, SCCs can originate in non-pulmonary organs and are collectively known as “extrapulmonary small cell carcinoma” (Remick et al., 1987; Remick and Ruckdeschel, 1992).

Extrapulmonary small cell carcinoma (EPSCC) often represents a diagnostic and therapeutic challenge. In 1930, it was first reported in the mediastinal glands without pathologic evidence of primary pulmonary involvement (Duguid and Kennedy, 1930). Since its first description, EPSCC has been reported in virtually all anatomical sites. The primary sites most frequently involved are gynecologic organs, especially the cervix; genitourinary organs, especially the urinary bladder and the prostate gland; the gastrointestinal tract, especially the esophagus, and head and neck region. In addition, SCC has been reported in the breast, thyroid, skin, and thymus gland. If the primary site remains undetected, these tumors are known as small cell carcinoma of unknown primary.

Limited data are available regarding its clinical behavior and outcome. The available literature is predominantly based on reviews of published cases or analysis of institutional data (Remick and Ruckdeschel, 1992; Vrouvas and Ash, 1995). In general, EPSCCs resemble their pulmonary counterparts with respect to purported histogenesis, morphology, and behavior. The clinico-pathological features, diagnosis, and general management of EPSCC are reviewed here, followed by a brief description of
small cell carcinoma specific to the more common sites.

EPIDEMIOLOGY

Small cell carcinoma arising from extrapulmonary sites represents 2–4% of all SCC (Remick and Ruckdeschel, 1992). Approximately, 1,000 cases per year have been reported in the United States, which represents an overall incidence between 0.1% and 0.4% of all cancers. Patients with EPSCC are generally middle-aged or older with more than 70% of patients being older than 50 years. Small cell carcinoma of the cervix is an exception and mainly affects younger females. Both genders are affected and predominance of either gender varies according to the primary site of involvement. For example SCC of esophagus, urinary bladder, and head and neck region are more common in men, whereas female preponderance has been noted in patients with SCC of gallbladder. Specific risk factors for the development of EPSCC have not been identified as yet. Although cigarette smoking appears to be associated with EPSCC especially of the head and neck region, it has not been clearly identified as a risk factor for EPSCC and the role of smoking in the development of this malignancy remains speculative.

Histogenesis

The pathogenesis of SCC is largely unknown and remains speculative. The earlier theory of origin of SCC from the APUD cells (a group of neuroendocrine cells) has been abandoned in favor of stem cell theory. It is now postulated that SCC originates from totipotent stem cells present in all tissues and capable of divergent differentiation (Frazier et al., 2007; Remick and Ruckdeschel, 1992). This theory offers explanation for the tumor heterogeneity and mixed morphology showing an admixture of SCC and various other epithelial cell types. Others have hypothesized that small cell component may arise from more differentiated tumors during the clonal evolution of a carcinoma as a late-stage phenomenon (Shaco-Levy et al., 2004). It is possible that there is more than one pathway for the development of these tumors.

PATHOLOGY

Extrapulmonary small cell carcinoma exhibits several neuroendocrine features characterized by the presence of enzymes such as dopa decarboxylase, calcitonin, neuron-specific enolase, chromogranin A, and CD56 (neural cell adhesion molecule). They are morphologically, immunohistochemically, and ultrastructurally indistinguishable from their pulmonary counterparts.

Light Microscopic Features

The histologic criteria are the same as those for the pulmonary neoplasm and the light microscopic features of EPSCC are indistinguishable from those of pulmonary SCC. The tumor is composed of sheets and nests of round to spindle-shaped cells with dense nuclei, granular nuclear chromatin, and minimal amounts of cytoplasm (Frazier et al., 2007). Nucleoli are absent or inconspicuous. The typical organoid architectural patterns of low-grade neuroendocrine neoplasms such as carcinoid tumor are generally absent. Mitotic rates are high and necrosis of individual malignant cell is common. It