Chronic administration of phenytoin and pleomorphic adenoma: A case report and review of literature

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Abstract:
Adverse drug effects that are uncommon or appear only on chronic administration of a drug may not be detected in clinical trials. This explains the need of strict post-marketing vigilance on drug use. Phenytoin administration has been shown in the literature to be associated with development of neoplasia (benign/malignant). In our knowledge current work represents the first case of pleomorphic-adenoma of sub-mandibular salivary gland developed following chronic phenytoin use. A 40 year old male having a history of head trauma twenty years back, had been on tablet phenytoin 100 mg thrice daily since then. One year back he noticed a small swelling in left sub-mandibular region and gradually increasing in size. FNAC and CECT revealed the diagnosis of pleomorphic-adenoma of sub-mandibular salivary gland. Other causes were ruled out. Surgical excision was performed successfully and continuing follow-up with no recurrence at the end of 6 months. Histo-pathogical examination of the tissue did not show any malignant changes.

Key words:
Chronic, phenytoin, pleomorphic adenoma, submandibular salivary gland

Treatment of a seizure disorder usually requires a long-term therapy with antiepileptic drugs. Adverse effects that are uncommon and/or appear on long-term use of a drug might not be detected in clinical trials (Hanley’s rule of 3) so there is a need of strict vigilance during their postmarketing period. Long-term administration of antiepileptic drugs has been reported to be associated with a number of benign/malignant neoplastic conditions. There are reports in the literature showing an association between long-term phenytoin use in humans and/or in animas and lymphoma, myeloma, neuroblastoma, liver tumors such as adenoma, cerebellar atrophy, and lymphadenopathy.

The present case report represents the first report of pleomorphic adenoma of submandibular salivary gland suspected to be induced by chronic phenytoin therapy.

Case Report
A 40-year-old male patient chronically maintained on phenytoin to treat seizure disorder, was diagnosed to have pleomorphic adenoma of left submandibular salivary gland for the last 1 year. The patient presented to surgery outpatient department with a chief complaint of swelling on the left side of the neck. The patient had a history of head trauma due to fall from a train with loss of consciousness and seizures but not of any bleed from ear, nose or throat, 20 years back. The patient had undergone some head surgery (probably craniotomy). The history of surgical procedure was unreliable because of unavailability of old records. After this, the patient was prescribed tablet phenytoin 100 mg thrice a day to manage seizure disorder, and the patient has been taking the same for the last 20 years. One year back patient noticed a small pea size swelling on the left side of the neck. The swelling had been increasing gradually in size since then to reach the size of a lemon at the time of presentation with relatively rapid growth in last month. Swelling was not associated with local pain, fever, anorexia, weight loss, cough with sputum, dyspepsia, or breathlessness. Besides above there was no history of any other chronic medical or surgical illness. On examination, patient was conscious and well oriented. His pulse rate was 76 beats/min, and blood pressure was 110/70 mm Hg. There was a
visible around 3 cm × 3 cm, nontender swelling present in the left submandibular region. The overlying skin was without any redness, scar, sinus, fistula, or dilated and engorged vein. The swelling was mobile in both the directions and had no intraoral extension. It was not attached to underlying muscle and overlying skin. Local temperature was comparable to rest of the body temperature. There was no facial weakness and tongue deviation. Respiratory, cardiovascular, and central nervous system examinations were within the normal limits. Hematological (Hb 12.9 g/dL, total leukocyte count 7880 cells/µL, platelet 3.71 lac/µL) and biochemical (blood urea 28 mg/dL, serum creatinine 0.8 mg/dL, alanine aminotransferase 35 IU/L, aspartate aminotransferase 23 IU/L, alkaline phosphatase 176 IU/L, total bilirubin 0.5 mg/dL, Na+ 136 mEq/L, K+ 3.9 mEq/L) parameters were within the normal limits. Tri-dot and Mantoux tests were negative. Electrocardiogram and chest X-ray were also within the normal limits.

Fine needle aspiration cytology of the swelling, done on September 14, 2015, revealed pleomorphic adenoma of the left submandibular salivary gland.

Contrast-enhanced computed tomography neck showed heterogeneously enhancing mass lesion in the left submandibular region measuring 37 mm × 30 mm × 27 mm. Fat plane with parotid and surrounding muscles were maintained, no stranding seen. Ultrasound correlation showed well-defined hypoechoic mass in the left submandibular region medial to sternocleidomastoid muscle and anterior to carotid vessels, however, anterior part of submandibular gland appeared normal. For management of the condition submandibular gland excision was planned.

After the patient was declared fit, surgery was performed successfully with adequate postoperative care. Peroperative findings revealed enlarged submandibular salivary gland involving both the superficial and deep lobe with normal surrounding viscera. The sample was sent for histopathological examination which did not show any malignant changes. There has not been a recurrence of the swelling yet at the end of 6 months during continuing follow-up.

**Discussion**

Phenytoin is a widely prescribed antiepileptic medication for grand-mal epilepsy and focal seizures.[3] Phenytoin is also prescribed prophylactically to control seizures following serious traumatic head injury as in the present case.[4] Various known adverse effects on its short-term use include nystagmus, ataxia, diplopia, dysarthria, vertigo, etc., and on chronic use include cerebellar atrophy, gingival hyperplasia, folate deficiency, osteomalacia, hypersensitivity reactions, etc.[4]

Antiepileptic drugs have been reported to have neoplastic/carcinogenic potential.[5] Carcinogenicity studies of phenytoin in animals (rat and mice) have shown increased incidence of hepatocellular adenoma, hepatocellular-carcinoma, hepatoblastoma, hemangioma, hemangiosarcoma, kuppfer cell sarcoma, and skin pilomatrixoma.[5] Various case reports and nested case-control studies show increased risk of lymphomas in humans with phenytoin therapy.[5]

To our knowledge, this is the first case report showing the development of pleomorphic adenoma of left-sided submandibular salivary gland after chronic intake of phenytoin.

Two mechanisms by which phenytoin may cause neoplasia have been suggested: (a) Promoting mechanism, i.e., phenytoin directly does not act as a carcinogen, but it induces CYP enzymes which convert xenobiotics into procarcinogenic agents (b) inhibition of gap-junction intercellular communication which inhibits regulates the growth of surrounding cells.[3,4] The exact mechanism of phenytoin to induce this pleomorphic adenoma is to be elucidated.

We tried to relate the drug exposure with development of pleomorphic adenoma using the WHO-Uppsala Monitoring Centre (UMC) causality assessment scale and Naranjo adverse drug reaction probability assessment scale. Causality was “possible” according to WHO-UMC scale whereas it is “probable” as per Naranjo scale.

This case report discloses one of the possible uncommon adverse effects of phenytoin which could be kept in mind while managing such a case. However, confirmation requires a number of such reports and large long-term cohort studies.

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**Conflicts of Interest**

There are no conflicts of interest.

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