The patient was started on antitubercular treatment (ATT) empirical enhanced computed tomo. Chest X-ray revealed left upper lobe effusion (Fig. 1 and contrast-enhanced computed tomography (CECT) chest were suggestive of lung cancer metastasizing to bone. Bone scan showed multiple metastases. His first chemotherapy cycle was started in March 2014 with cisplatin 125 mg and pemetrexed 850 mg intravenous (IV) along with the IV infusion of 4 mg zoledronic acid. A total of eight cycles were given comprising one cycle once a month and during the course of treatment patient was stable and fine without any symptoms. In September 2014, he complained of severe dyspnea; on examination, massive left-side pleural effusion was noted. Intercostal drain was put, and fluid was drained along with pleurodesis using bleomycin. The patient recovered within a span of 2 months and fine without any symptoms. In January-February 2015, routine investigations unfolded the deranged liver functions, ascertained by markedly elevated liver enzymes (Figs. 3 and 4) and zoledronic acid was suspected as the underlying cause of hepatic dysfunction. In February 2015, zoledronic acid was stopped (dechallenge) and never re-administered (rechallenge), gradually patient showed recovery and liver function test (LFT) became normal within a span of 2 months (Fig. 3 and 4).

INTRODUCTION
Cancers are the leading cause of mortality worldwide with the most common cancers responsible for half of the global incidence is lung, breast, colorectal, prostate, stomach, and liver. Worldwide among men, lung cancer is more prevalent, whereas breast cancer typically predominates amid women. Overall, lung cancer is the most commonly diagnosed cancer worldwide with about 1.8 million new cases diagnosed every year with 1.6 million deaths [1]. Every year in India around 63,000 new lung cancer cases are reported [2]. Among the various histological subtypes of lung cancer, trends show increased incidence of adenocarcinoma among both men and women [3]. Pemetrexed-containing chemotherapeutic regimens are now widely used compared to taxanes, platinum-based, and other chemotherapeutic agents [4]. Bone is a common site of metastasis and incidence of lung cancer metastasizing to bone is around 36% [5]. Zoledronic acid, a bisphosphonate is very effective in the treatment of bone metastasis [6]. Adverse effects associated with it include flu-like symptoms, nausea, arthralgia, renal tubular acidosis, hypocalcemia, esophageal irritation, and fatigue. Hepatic dysfunction exclusively due to zoledronic acid is a very rare occurrence with only two case reports so far brought to the light of scientific committee from Europe and China. Until now, no such report has been mentioned from the Indian subcontinent. Henceforth, we are reporting a case of zoledronic acid-induced liver injury.

CASE REPORT
A 47-year-old male diagnosed as adenocarcinoma of the lung and received 8 cycles of chemotherapy comprising intravenous administration of cisplatin 125 mg, pemetrexed 850 mg along with zoledronic acid 4 mg. After the completion of the 8th cycle, the liver enzymes were found to be markedly elevated, evincing zoledronic acid as the cause for hepatotoxicity. The case details were taken from the patient’s medical record along with the biochemical test reports and radiographic images. The causal association was confirmed using Naranjo’s algorithm and Roussel Udaf Causality Assessment Method (RUCAM). After the uneventful chemotherapy, patient’s liver function tests (LFT) were abnormal. There was an elevation in the aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and direct bilirubin. The causal relationship was established using Naranjo’s algorithm (score-6) and RUCAM (score-5), displayed a “probable” and “possible” association. Hartwig’s severity scale and Thornton’s preventability scale displayed the adverse drug reaction to be moderately severe and not preventable, respectively. The zoledronic acid was stopped and never readministered. The LFTs assumed normal after a span of 2 months. The mechanism underlying hepatotoxicity due to zoledronic acid remains elusive. Zoledronic acid can induce acute phase response mediated by active production of interleukin-6, tumor necrosis factor alpha, and pro-inflammatory cytokines from the T-cells and macrophages. Vigilant monitoring along with timely assessment and management can prevent the occurrence of irreversible liver damage. Henceforth, we would like to report the rare incidence of drug induced hepatic damage due to zoledronic acid. Henceforth, we would like to report the rare incidence of drug induced hepatic damage due to zoledronic acid.
breast, kidney and lung [5] and incidence of lung cancer metastasizing to bone is found to be high [5]. Irrespective of whether the bone lesions are osteolytic or osteoblastic, zoledronic acid, a bisphosphonate class of drug is very effective in the treatment of bone metastasis as well in the prevention of metastasis seen with advanced cancers [6].

Bisphosphonates are pyrophosphate analogs; act by binding to the hydroxyapatite and thereby accumulating in the bone and preventing osteoclastic activity. The underlying mechanism of action in bones is it first binds to the surface of bone, then gets adsorbed on mineral surfaces of the bone and later internalizing into osteoclasts, finally leading to disruption of the bone-resorbing activity of osteoclasts [8]. In addition, it suppresses osteoclast maturation as well as brings about apoptosis. In a case of metastatic bone lesions, bisphosphonates inhibit cancer cell bone matrix interaction, furthermore will hinder the cancerous invasion of bones [9], making bisphosphonates the drug of choice to treat both osteolytic and osteoblastic metastatic lesions.

Bisphosphonates have become the popular choice in the past decade to treat postmenopausal, glucocorticoid-induced and transplant-associated osteoporosis, Paget’s disease and metastatic bone lesions due to osteotropic cancers [10]. The adverse effect profile of this class of drug includes upper gastrointestinal side effects-esophagitis, esophageal erosions, gastric ulcers; influenza-like symptoms-fever, arthralgia, fatigue, bone pain; fragile fractures of atypical nature predominantly involving femur; osteonecrosis of jaw; atrial fibrillation; renal damage-acute tubular necrosis and focal segmental glomerulosclerosis [11]. Whereas, hepatotoxicity is a very rare side effect seen due to bisphosphonates with only a few case reports to support this evidence [12-15]. As per the literature search, hepatic damage solely due to zoledronic acid is an unusual outcome; especially in the absence of any pre-existing liver disease, concomitant medication implicated to cause hepatotoxicity, evidence in favor of zoledronic acid as an attributing factor for hepatic dysfunction is scanty and so far only two case reports have been reported [16,17]. A pre-clinical study carried in rats has shown biopsy-confirmed hepatotoxicity due to zoledronic acid administration [18]. Earlier two case reports have been noted in female patients diagnosed with postmenopausal osteoporosis and Paget’s disease, demonstrating the transient rise in liver enzymes. No serious liver injury was implicated [16,17]. Compared to earlier published cases, by our knowledge, it is the first report of zoledronic acid associated hepatic injury in a male patient suffering from cancer. Through literature search displayed no report of zoledronic acid associated liver injury from Indian subcontinent till date.

The mechanism by which zoledronic acid causes hepatotoxicity remains elusive, yet some theories to support this uncommon finding can be stated as follows: First, the bisphosphonates induce acute phase response mediated by active production of interleukin-6, tumor necrosis factor alpha (TNFα), and pro-inflammatory cytokines from the T-cells and macrophages. These cytokines mainly TNFα has been suspected to explain drug induced-liver injury; TNFα is involved in the activation of various intracellular and apoptotic pathways, which inhibit liver cell proliferation. Moreover, TNFα along with some other pathways - IκB kinase, reactive oxygen species, and stress-activated protein kinases/Jun amino-terminal kinases pathway promotes apoptosis of liver cells [19,20]. Second, amino-bisphosphonate like

\[
\begin{align*}
\text{Liver enzyme levels (IU/L)} \\
\text{AST: Aspartate aminotransferase, ALT: Alanine transferase, ALP: Alkaline phosphatase}
\end{align*}
\]
Bisphosphonates inhibit prostate and breast carcinoma cell
it will be wise to do continuous monitoring of LFTs during zoledronic
a causal relationship was successfully established in this case, hence
bisphosphonates particularly zoledronic acid is a rare occurrence; since
Drug-induced hepatotoxicity due to nitrogen-containing
CONCLUSION
induced injury [28].
within 30 days following cessation of suspected drug and it is drug-
improvement observed in laboratory values of liver enzymes following
done nor rechallenge of zoledronic acid was executed. Moreover, rapid
liver injury and it is very hard to differentiate. Neither liver biopsy was
The greater rise in ALP can be attributed to both bone metastasis and
primary biliary cirrhosis, sclerosing cholangitis were excluded out.
Every drug has its own particular mechanism implicated for more-
recent history of hypotension, shock or ischemia within past 2 weeks,
5 years, concomitant hepatotoxic drugs, hepatitis B, hepatitis C, a
there was a sudden elevation in aspartate aminotransferase, alanine
In this case, after duration of 10 months of uneventful chemotherapy,
there was a sudden elevation in aspartate aminotransferase, alanine
transaminase (ALT), alkaline phosphatase (ALP), and direct bilirubin
Figs. 3 and 4) in January 2015. Administration of zoledronic acid was
stopped and it was not re-administered; though calcium tablets were
continued. Later during follow-up, laboratory investigations exhibited
liver enzymes within the normal range. Furthermore, the causal
relationship was established using Naranjo’s algorithm (score - 6) and
Roussel Ulcinf Causality Assessment Method (score - 5), displayed a
“probable” and “possible” association [21-23]. Furthermore, Hartwig’s
severity scale [24,25] and Thornton’s preventability scale [26]
demonstrated adverse drug reaction to being moderately severe and
not preventable, respectively. The other risk factors-alcohol use, age
>55 years, concomitant hepatotoxic drugs, hepatitis B, hepatitis C, a
recent history of hypotension, shock or ischemia within past 2 weeks,
primary biliary cirrhosis, sclerosing cholangitis were excluded out.
Every drug has its own particular mechanism implicated for more-
or-less liver injury. In view of less prominent features in favor of liver
injury, asymptomatic ALT ≥8 N or a ≥1.5-fold elevated direct bilirubin
along with raised ALT levels can be considered as a diagnostic [27].
The greater rise in ALP can be attributed to both bone metastasis and
liver injury and it is very hard to differentiate. Neither liver biopsy was
done nor rechallenge of zoledronic acid was executed. Moreover, rapid
improvement observed in laboratory values of liver enzymes following
drug withdrawal raises the susceptibility of drug-induced liver damage.
Consensus supports if there is a decline in >50% of liver enzymes
within 30 days following cessation of suspected drug and it is drug-
induced injury [28].

CONCLUSION
Drug-induced hepatotoxicity due to nitrogen-containing
bisphosphonates particularly zoledronic acid is a rare occurrence; since
a causal relationship was successfully established in this case, hence
it will be wise to do continuous monitoring of LFTs during zoledronic
acid administration. Every individual drug has its own trademark
pattern of liver injury and with only handful previous case reports to
support zoledronic acid induced hepatic damage; it should be advised
to identify the adverse event early and preventive actions taken soon
to delay further progression. If additional studies are done in regard
to pharmaco kinetic properties of zoledronic acid in genetically
predisposed population, it will add a valuable tool to do a confirmatory
diagnosis. To sum up, vigilant monitoring along with timely assessment
and management can prevent the occurrence of irreversible liver
damage.

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