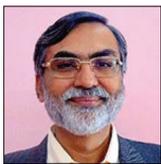


Editorial

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The case report by Harikrishnan *et al.* is interesting because their patient with adenocarcinoma of lung had an epidermal growth factor receptor (EGFR) exon 19 deletion at initial presentation and subsequently demonstrated EGFR exon 20 insertion mutation at recurrence.^[1]

Next-generation sequencing (NGS) showed activating mutation of exon 19 deletion but no other targetable genetic alterations. The logical initial therapy consisted of Gefitinib, the first-generation EGFR TKI inhibitor.^[2] It is not surprising that the patient responded (partial response) at 6 months and subsequently developed disease progression – a common occurrence after a period of 12–18 months.^[3]

Repeat NGS from the brain metastasis revealed EGFR, p. Asn 3 771_His773dup (exon 20 insertions). The originally identified exon 19 deletion was no longer seen. Interestingly, there was no evidence of T790M mutation, a common cause of EGFR TKI resistance. Again the authors correctly changed the systemic treatment to Afatinib, an effective second-generation EGFR TKI inhibitor.^[4]

In this editorial, we would like to focus on three other aspects of the case.

AGE AT PRESENTATION

This patient was 47 years old when he was confirmed to have a diagnosis with lung cancer. Since the solitary pulmonary nodule (SPN) was identified 3 years earlier, his age would have been 44 years. A large study of 1862 consecutive patients with lung cancer between January 2008 and March 2018 (10 years) has been reported by All India Institute of Medical Sciences, the premier institution in New Delhi.^[5] It documented a mean age of 59 years (range 46–70 years), which is similar to that seen elsewhere as well as remains unchanged over the years.^[6,7] While younger patients with lung cancer have been documented, this patient developed the disease at an age which is an outlier (<2.35%) for Gaussian distribution. Could be the reason to be linked to the comorbidities? (vide infra).

COMORBIDITIES

This young man had rheumatic heart disease, moderate aortic regurgitation, and subclinical hypothyroidism. These are significant comorbidities, the former two not commonly seen in today's day and age.

Several publications have documented a high risk for the development of cancers in those who have rheumatic diseases.^[8] Some commonly recognized paraneoplastic syndromes include

hypertrophic osteoarthropathy, carcinomatous polyarthritis, palmar fasciitis, vasculitis, polymyalgia rheumatica, erythromelalgia, amyloidosis, remitting seronegative synovitis, panniculitis, multicentric reticulohistiocytosis, dermatomyositis, and lupus like and scleroderma like syndromes.^[8]

In addition, some autoimmune and rheumatic diseases have a direct real increased risk of malignancies. The exact cause is not known. Factors implicated include immunosuppressive therapy, Epstein bar virus, smoking, and even genetic susceptibility. For patients with rheumatoid arthritis, the risk of developing a malignancy is 2–3 times higher than in the normal population.^[9] Interestingly, among solid tumors, this increased risk has been documented only for lung cancer.

Levels of many tumor-associated antigens (e.g., CA 15-3, CA 125, and CA 19-9) have been reported to be high in the serum of patients with autoimmune diseases as well as in their tumor cells.^[10]

Drugs used in the treatment of rheumatic diseases can also lead to the development of cancers (e.g., cyclophosphamide, methotrexate, cyclosporine, and azathioprine).^[11] Meta-analysis shows that this risk could be 3.3 times higher than the normal population.^[12] We do not have the details of whether this patient received any such medications.

Fortunately, a large and retrospective study conducted from 2003 to 2019 confirms that the survival of lung cancer patients who also have a rheumatic disease ($n = 177$) is not inferior to the cohort without such comorbidities ($n = 219$).^[13]

This was true for OS, DFS, and the rate of recurrence of locoregional disease. Of concern was the fact that more patients with the autoimmune disease did not receive standard of care. Would that imply a protective role of the latter in cancer patients?^[14]

WAS THERE A DELAY IN THE CORRECT DIAGNOSIS?

This patient was first identified to have SPN – which would have been Stage I disease if it was NSCLC. Three years later, the lesion has increased in size, and a PET CT scan indicated that, now, the stage was at least III (increased uptake in mediastinal, hilar, right upper paratracheal, and subcarinal lymph nodes). It was unfortunate that multiple biopsies were inconclusive, and finally, a wedge resection of the lung SPN was necessary to confirm the diagnosis of NSCLC. By refusing to undergo lobectomy (as recommended by his doctors), the patient lost the chance of potentially curative therapy. This is a global problem that is difficult to tackle.^[15]

CONCLUSION

This case report of lung cancer has several unique features. Young age at diagnosis, associated comorbidities of significance (like a rheumatic disease), delays in diagnosis in a case of SPN, patient's refusal to undergo potentially curative surgery, and the transition from EGFR exon 19 mutation to EGFR exon 20 insertion mutation.

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