



Case Report

Pioglitazone Induced Carcinoma of Urinary Bladder: A Case Report

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ABSTRACT

Background: Pioglitazone is widely prescribed oral hypoglycaemic thiazolidinediones acting through Peroxisome Proliferators Activated Receptor gamma (PPAR γ) as agonist. Apart from potent anti-hyperglycaemic action by improving insulin sensitivity, it also has positive effects on lipid metabolism and endothelial function. Controversies about use of Pioglitazone have been raised with regard to risk of bladder cancer. Hence recently drug was banned in India, but again ban was revoked for its use with special precautions. So there is a lot of debate about benefit to risk ratio of this drug. With this background we are presenting a case of carcinoma of urinary bladder developed in type 2 diabetes mellitus (T2DM) patient who was receiving Pioglitazone for glycemic control.

Case presentation: A 65 year old man was admitted to our centre for tumor in urinary bladder. He was diagnosed as a case T2DM 8 year's back at his village and started therapy with Metformin. After 2 years Pioglitazone was added for glycemic control. He received Pioglitazone in combination with Metformin for 6 years and then diagnosed urinary bladder cancer. First we shifted him from Pioglitazone to Mixtard Humiinsulin therapy. We managed him by transurethral resection of bladder tumour followed by 6 cycles of intravesical Mitomycin 40 mg weekly chemotherapy regimen. After completion of total treatment he is in remission period for 11 months.

Conclusion: To study long term safety of Pioglitazone, large population based prospective studies are required. But till that time physicians should pay careful attention to assess the possibility of bladder cancer in patients receiving Pioglitazone.

Introduction

Pioglitazone is widely prescribed oral hypoglycaemic thiazolidinediones acting through Peroxisome Proliferators Activated Receptor gamma (PPAR γ) as agonist¹. Apart from potent anti-hyperglycemic action by reducing insulin resistance, it also has favorable effects on lipid metabolism and endothelial function. On one side there is supporting evidence of cardio-protective role of Pioglitazone whereas some researchers showed its association with bladder cancer².

Controversies about use of Pioglitazone have been raised with regard to risk of bladder cancer. Hence recently drug was banned in India, but again ban was revoked for its use with special precautions. So there is a lot of debate about benefit to risk ratio of this drug. With this background we are presenting a case of carcinoma of urinary bladder developed in T2DM patient who was receiving Pioglitazone as a first line therapy for glycaemic control.

Case Presentation

A 65 year old man was referred to our centre with chief complaints of increased frequency, burning micturition and hematuria since last one year. He was known case of T2DM since 8 years with oral hypoglycemic agents. For the first 2 years he was managed with Metformin only. But because of poor glycaemic control Pioglitazone was added and this combination resulted in good glycaemic status. Also he was hypertensive since one year. He was tobacco chewer since 20 years. His family and past history was unremarkable. His general physical examination was nonsignificant except tenderness in suprapubic region. Superficial lymph nodes were not palpable.

Urine analysis showed microscopic hematuria. Initially an empirical course of antibiotics was administered despite of

which complaints did not relieve. Routine hematological examination including coagulation profile was within normal limit except for mild hypochromic microcytic anemia (Hemoglobin 9.0 gm/ dl). Serum biochemical and electrolyte parameters were within stipulated range.

Ultrasonography examination of pelvis revealed a large hypo echoic exophytic nonmobile polypoidal mass measuring 8x6x4 cm arising from lateral wall of urinary bladder. This suggested presence of space occupying lesion in bladder. A detailed radiological computed tomography of abdomen and pelvis revealed a thickened wall of the urinary bladder. (Figure1.)

We proceeded for urethrocystoscopy which revealed a mass in urinary bladder originating from right lateral wall. (Figure 2)

Biopsy was taken from the growth and sent for histopathological examination which confirmed diagnosis of papillary transitional cell carcinoma of urinary bladder.

After thorough preoperative examination, we performed transurethral resection of bladder tumor. Then he received 6 cycles of intravesical chemotherapy with Mitomycin 40 mg every week. Patient is on regular follow up every three months since completion of treatment. He is in complete remission state for 11 months.

Discussion

Association of Pioglitazone use and bladder cancer was first reported in preclinical studies in US in 1999. Carlo Piccinni and associates analyzed association between anti-diabetic drugs and bladder cancer through adverse event recording. They reported 31 cases of bladder cancer in Pioglitazone users with significant ROR above 1³. The major correlation between Pioglitazone and bladder cancer is the duration of therapy >24 months of therapy

and cumulative dose of >28000 mg means 40 mg per day. But in India Pioglitazone is used in doses less than 15 mg per day with fewer side effects⁴. Our patient received 30 mg of Pioglitazone for more than 6 years. However, since the genetic makeup of Indians is different than the Caucasians, the risk of bladder cancer can occur even at lower dose.

FDA from USA issued guidelines about use of Pioglitazone. It should not be used in patients of active bladder cancer and with caution in patients with past history of bladder cancer⁵.

Recently Pioglitazone was suspended for use in India, which was later revoked. Now it is available with black box warning. Few European countries like Germany and Greece have already banned Pioglitazone for the risk of developing bladder cancer.

In ACT NOW trial Pioglitazone reduced risk of developing T2DM by 72% in prediabetes patients. Safety concerns for use of Pioglitazone are body weight gain, fluid retention, bone fractures, and bladder cancer⁶. Results of PROactive trial reported significant cases of bladder tumors in the Pioglitazone users versus placebo group (14 Vs 6; $P=0.069$)⁷. Californian longitudinal cohort study revealed increased risk of bladder cancer among Pioglitazone users (HR, 1.20; 95% CI, 0.9–1.5; $P>0.05$). But the risk was associated with use of Pioglitazone for more than 2 years. Recent French observational retrospective cohort study of 1 491060 patients documented a moderate, but significant, raised risk of bladder cancer among Pioglitazone users ($n = 155735$ $P = 0.01$) with a clear relationship between dose and duration of Pioglitazone treatment⁸.

A. Neumann *et al* reported significant association of exposure to Pioglitazone with bladder cancer incidence in France population based cohort study⁹. Azoulay L. and colleagues determined significant association of duration of Pioglitazone use with bladder cancer in nested case control study in a cohort

of 115727¹⁰. Ferrara A *et al* also found risk of bladder cancer in Pioglitazone users for more than 24 months¹¹. Bertrand Cariou and associates reviewed safety challenges during use of Pioglitazone and recommended the drug for the most insulin resistant candidates with increased waist circumference, low HDL-C levels and NAFLD. Also it exerts additional cardio-protective effect in high risk individuals with Diabetes Mellitus¹².

Awareness and counseling of the patient using Pioglitazone is very important. They should be insisted to report signs and symptoms of bladder cancer like blood in urine, pain during micturation, supra-pubic and back pain. Asymptomatic hematuria should be investigated with urological investigations promptly.

Conclusion

To study long term safety of Pioglitazone, large population based prospective studies are required. But till that time physicians should pay careful attention in appropriate patient selection to offer Pioglitazone for glycemic control. Risk factors for bladder cancer should be assessed before starting the drug and once started patients should be critically reviewed for the possibility of bladder cancer.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contributions and acknowledgements

Dr. Takalkar U V, Chinchole involved in diagnostic work up and surgical management, Asegaonkar S. B. and

Borundiya in data collection, investigations and manuscript preparation, Rote in glycemic management, Balaji in anesthetic management. Dr. Kodlikeri and Kulkarni contributed in patient's hospital care. Dr. Advani was concerned with medical oncology treatment.

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