CASE REPORT

Glioblastoma Multiforme in a Post Allogeneic Stem Cell Transplant Patient. A Case Report and Literature Review of Post Transplant Neurological Tumors

Abhijeet P. Ganapule · Sunita Susan Varghese ·
Geeta Chacko · I. Aparna · Auro Viswabandya

Received: 24 April 2014 / Accepted: 5 January 2015 / Published online: 14 January 2015
© Indian Society of Haematology & Transfusion Medicine 2015

Abstract Seventeen year old boy, a case of relapsed acute lymphoblastic leukemia 10 years post allogeneic transplantation, presented to us with acute onset of right hemiparesis. The imaging revealed contrast enhancing lesion in the frontal lobe, biopsy of the same was consistent with glioblastoma multiforme (GBM). He had received total body irradiation (TBI) based conditioning regimen prior to transplant. GBM was treated with left parietal craniotomy and parietal excision of tumour, followed by radiation therapy with concurrent and adjuvant chemotherapy. Disease progressed while was on adjuvant chemotherapy and patient succumbed to his illness 8 months after the diagnosis of GBM. We report here a here unusual case of GBM in a post transplant patient who received TBI based conditioning regimen.

Keywords Relapsed ALL · Post transplantation · Glioblastoma multiforme (GBM) · Total body irradiation (TBI)

Introduction

Allogeneic stem cell transplant is an effective treatment for leukemia as well as other malignancies and non malignant haematological conditions [1]. Secondary malignancies (SM) are seen after allogeneic stem cell transplantation especially with the conditioning regimen which is TBI or high dose chemotherapy based [1]. The cumulative incidence of secondary tumors in post transplant period is 1 % at 10 years, 2.2 % at 15 years and 3.3 % at 20 years [2].

Case Report

Five year old boy was diagnosed in our hospital as Pre B cell acute lymphoblastic leukemia (ALL) and was initiated on Berlin Frankfurt and Munich Pediatric (BFM) ALL Protocol. He had received cranial radiation 1,800 cGy in 12 fractions during the ALL chemotherapy protocol. When he was on maintenance chemotherapy he had CNS and medullary relapse, for which he was started on relapse BFM ALL protocol. He achieved morphological remission after salvage chemotherapy and underwent allogeneic stem cell transplant at the age of 6 years with his human leukocyte antigen (HLA) matched sister as the donor. He was given Cyclophosphamide and TBI (12 Gy in 6 fractions) as conditioning regimen prior to transplant. Post transplant he had chronic limited graft versus host disease (GVHD) involving the skin. The chronic limited GVHD was controlled with steroids and cyclosporin. He also suffered from multidrug resistant pulmonary tuberculosis 10 years post transplant for which he was treated with appropriate drugs and duration. Ten years post allogeneic transplant he presented with holocranial headache and weakness in the right upper limb and lower limb of 1 month duration. On clinical examination, he

A. P. Ganapule · A. Viswabandya (✉)
Department of Haematology, Christian Medical College and
Hospital, Ida Scudder Road, Vellore 632004, Tamil Nadu, India
e-mail: aurov@cmcvellore.ac.in

S. S. Varghese
Department of Radiotherapy, Christian Medical College and
Hospital, Ida Scudder Road, Vellore 632004, Tamil Nadu, India

G. Chacko
Department of Pathology, Christian Medical College and
Hospital, Ida Scudder Road, Vellore 632004, Tamil Nadu, India

I. Aparna
Department of Radiology, Christian Medical College and
Hospital, Ida Scudder Road, Vellore 632004, Tamil Nadu, India

had right hemiparesis. The MRI of the brain showed a well defined heterogeneous contrast enhancing mass measuring 5.5×5.4 cm in the left inferior frontal region (Fig. 1). Subtotal excision of the lesion was done and the surgical pathology specimen showed a hypercellular tumor composed of sheets of small to medium sized cells with moderately pleomorphic hyperchromatic nuclei some with prominent nucleoli and scant to moderate amount of eosinophilic cytoplasm. Several multinucleate tumor cells and few cells with a rhabdoid morphology were seen (Fig. 2). On immunohistochemistry these tumor cells were strongly positive for GFAP and S100 with dot like and membranous immunoreactivity for CD99 and focal dot like reactivity for cytokeratin (Fig. 3). Cells were negative for LCA, synaptophysin, CD2, KD-1, EMA and desmin. A diagnosis of GBM was made based on the morphological and immunohistochemistry markers.

He was treated with conformal radiation therapy delivering 54 Gy in 30 fractions to the planning target volume (PTV), five fractions per week. He also received concurrent chemotherapy with T. Temozolomide (75 mg/sq m) for

Fig. 2 Photomicroscope illustrating small to medium sized tumor cells with pleomorphic nuclei, including multinucleated forms (Haematoxylin and Eosin $\times 600$)

42 days during RT. Evaluation of disease status 1 month post RT showed stable disease. He was started on adjuvant chemotherapy with T. Temozolomide as per the Stupp

Fig. 1 T2W axial (a), T1W sagittal (b), post Gadolinium T1W axial (c) and sagittal (d) images show a heterogenous mass in posterior and inferior aspect of left frontal lobe (arrows) which is hyperintense on T2W images, hypointense on T1W images with thick nodular irregular peripheral enhancement and central necrotic nonenhancing areas (asterisk in c and d). Necrotic areas are bright on T2W images (asterisk on a). Associated mass effect is seen as effacement of the adjacent sulci and mild midline shift to the right

Fig. 3 Photomicroscope illustrating diffuse immunopositivity for GFAP in tumor cells (Avidin Peroxidase ×600)

et al. protocol [3]. After three cycles of adjuvant Temozolamide, he had recurrent right paraparesis with holocranial headache. He was unable to carry out his activities of daily living. MRI brain with contrast showed disease progression; concurrently he also developed a right axillary mass. The FNAC from the axillary mass was reported as spindle cell neoplasm. Considering the dismal prognosis the patient and family decided to continue on best

supportive care only. He succumbed to his illness with a survival of 8 months after the diagnosis of GBM.

Discussion

Among the late effects of the stem cell transplant, SM are of particular concern. SM are commonly classified into three groups (1) Post transplant lymphoproliferative disorder (2) Myelodysplasia and acute myeloid leukemia (3) Solid tumours (ST) [2]. The risk factors noted for solid tumors are; younger age at transplantation, exposure to radiation as part of conditioning regimen and chronic GVHD [4]. Thus one needs to be judiciously using radiation in non malignant conditioning, as there have been reported cases of glioblastoma post radiation for benign lesion like tinea capitis, acoustic neuroma [5, 6]. In order to define tumor as radiation induced Cahan proposed criteria in 1948 [7]. Cahan criteria includes; (1) the tumor must originate in the previously irradiated region; (2) there must be a sufficiently long interval from irradiation and the onset of tumor; (3) the histology of the tumor must be different from the primary one; (4) the patient must not have genetic predisposition to cancer [7]. The neurological tumors (NT) reported as ST in post transplant period includes primitive neuro-ectodermal tumor (PNET), ependymoma, medulloblastoma, glioma and

Table 1 -Neurological tumors presenting as secondary malignancy post stem cell transplant

S. no.	Study	Second neurological tumors	Number	Co-relation with age of TBI given with secondary tumor	TBI Fractionated(F)/single fraction (SF) association with secondary tumor
1	Witherspoon et al. [7]	Glioblastoma multiforme(GBM)	6	Age <10 years	950–1,000 cGy SF
2	Curtis et al. [1]	Astrocytoma	4	Age <10 years	SF >10 Gy
		GBM	6		F >13 Gy
		Primitive neuroendocrine tumors	1		
3	Baker et al. [8]	Astrocytoma	1	Age <10 years	No association
		Ependymoma	1		
		GBM	1		
		Primitive neuroendocrine tumors	1		
4	Kolb et al. [9]	GBM	3	Age <10 years	No association
5	Pommier et al. [10]	Medulloblastoma	1	6	12
		GBM	1	5	12
		Brain lymphoma	1	4	12
6	Ferry et al. [11]	Glioma	1	No association	SF (dose not mentioned)
		GBM	1		
		Primitive neuroendocrine tumors	1		
7	Kim et al.[12]	GBM	1	No association	No association
8	Sanders et al. [13]	GBM	1	7	1,000 cGy single fraction and 2,400 cGy prophylactic cranial irradiation
9	Our case	GBM	1	6	12 Gy(fractionated) and cranial RT 1,800 cGy

CNS lymphoma [1, 8–14]. There is also correlation between NT and high dose TBI, defined as >1,000 cGy single fraction or 1,300 cGy in fractionated doses compared to either no or low dose irradiation [1, 8, 11, 12, 14] [Table 1]. Witherspoon et al. summarises the incidence of SM in 5,000 post allogeneic stem cell transplant patients. Of the 103 SM, six were NT [8]. All six NT were GBM [8]. Curtis et al. studied incidence of SM in 19,229 patients who underwent allogeneic stem cell transplant, total 80 secondary cancers were documented in these patients [1]. Of these 80 SM, there were 11 spinal cord and brain tumors [1]. The 11 spinal and brain tumors consisted of four astrocytomas, six GBM and one PNET [1]. Baker et al. evaluated incidence of SM in 3,372 patients of allogeneic stem cell transplantation, 147 patients had SM, of which four were NT, one each of astrocytoma, ependymoma, glioma and PNET [9]. Kolb et al. on behalf of The European group for blood and marrow transplantation (EBMT) studied secondary cancer in 1,036 patients post stem cell transplantation [10]. There were total 53 patients who had SM of which three had NT and all three had GBM [10]. Pommier et al. studied 240 children who underwent allogeneic stem cell transplantation with TBI as conditioning regimen [11]. There were 14 cancers in 13 patients, of which three were NT [11]. The three NT included one each by medulloblastoma, GBM and CNS lymphoma [11]. Ferry et al. studied long term outcomes after allogeneic stem cell transplantation for 112 children with haematological malignancies; eight patients had SM of which three were NT, one each of glioma, GBM and PNET cerebellum [12].

Kim et al. reported a case of GBM in a patient of acute myeloid leukemia, which occurred 4 years after the autologous stem cell transplantation with TBI based conditioning [13]. Sanders et al. also reported GBM in a post allogeneic stem cell transplant patient, where TBI was used as a conditioning regimen [14].

In our case the age of the patient was 6 years when he received fractionated TBI (12 Gy in 6 fraction) as pre-transplant conditioning. He had received cranial irradiation 1,800 cGy in 12 fractions as per the protocol. He was diagnosed to have GBM after 10 years of transplant; this is time frame during which incidence of secondary tumour is more.

Conclusion

Among NT presenting as SM, glioblastoma multiforme is probably the most common. There is strong correlation seen in various studies between development of NT and age of the recipient at the time of transplant. The

development of NT is correlated to total dose of radiation and whether it was fractionated or not. The incidence of NT as secondary malignancy post stem cell transplantation is rare and reporting these cases will help us to know actual incidence.

References

1. Curtis RE, Rowlings PA et al (1997) Solid cancers after bone marrow transplantation. *N Engl J Med* 336:897–902
2. Majhail Navneet S et al (2011) Secondary cancers following allogeneic haematopoietic cell transplantation in adults. *Br J Haematol* 154(3):301–310
3. Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352(10):987–996
4. Majhail NS, Brazauskas R, Rizzo JD, Sobecks RM, Wang Z, Horowitz MM (2011) Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning. *Blood* 117(1):316–322
5. Balasubramaniam A, Shannon P, Hodaie M et al (2006) Glioblastomamultiforme after stereotactic radiotherapy for acoustic neuroma: case report and review of the literature. *Neuro-Oncology* 9:447–453
6. Slavati M, Frati A, Russo N et al (2003) Radiation-induced gliomas: report of 10 cases and review of the literature. *Surg Neurol* 60:60–67
7. Cahen WG, Wooddard HQ, Hinginbotham NL, Stewart FW, Coley BL (1948) Sarcoma arising in irradiated bone: report of 11 cases. *Cancer* 154:1431–1438
8. Witherspoon RP, Deeg HJ, Fischer L, Schoch G, Storb R et al (2000) Secondary malignancies after allogeneic or autologous marrow transplantation. In: Ruther U, Nunnensiek C, Schmoll H-J (eds) *Secondary neoplasm following chemotherapy, radiotherapy, and immunosuppression*, Contrib Oncol, vol 55. Karger, Basel, pp 203–224
9. Baker KS, Defor TE, Burns LJ et al (2003) New malignancies after blood o marrow stem cell transplantation in children and adults: incidence and risks factors. *J Clin Oncol* 21(7):1352–1358
10. Kolb HJ, Socie Gerard, Duell Thomas, Lint Maria TheresaVan, Tichelli Andere, Apperley Jane F et al (1999) Malignant neoplasm in long-term survivors of bone marrow transplantation. *Ann Intern Med* 131(10):738–744
11. Pommier Pascal, Sunyach Marie Pierre, Pasteuris Caroline et al (2009) Second cancer after total body irradiation in childhood. *Strahlenther Onkol* 185:13–16
12. Ferry C, Gemayel G, Rocha V, Lobopin M et al (2007) Long term outcomes after allogeneic stem cell transplantation for children with haematological malignancies. *Bone Marrow Transplant* 40:219–224
13. Kim Eun-Oh, Kim Hee-Je, Min Woo Sung et al (2011) Secondary glioblastoma multiforme following autologous haematopoietic stem cell transplantation in a patient with acute myelogenous leukemia. *Cancer Res Treat* 43(3):195–198
14. Sanders J, Sale GE, Ramberg R, Clift R, Buckner CD, Thomas ED (1982) Glioblastoma multiforme in a patient with acute lymphoblastic leukemia who received a marrow transplant. *Transplant proc* 14(4):770–774