ISSN: 2325-7075 Volume 9, Number 4, April 2020

Scientific Research Publishing

Case Reports in Clinical Medicine

ISSN: 2325-7075

https://www.scirp.org/journal/crcm

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ISSN Print: 2325-7075 ISSN Online: 2325-7083
https://www.scirp.org/journal/crcm

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Case Reports in Clinical Medicine, 2020, 9, 81-114
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

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Volume 9 Number 4 April 2020

Case Reports in Clinical Medicine (CRCM)
Journal Information

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Case Reports in Clinical Medicine, 2020, 9, 81-86
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Thoracic Air Leak Syndrome: A Rare and Fatal Complication of Allogeneic Stem Cell Transplant

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How to cite this paper: Sakkat, A., Patel, M. and Haider, S. (2020) Thoracic Air Leak Syndrome: A Rare and Fatal Complication of Allogeneic Stem Cell Transplant. *Case Reports in Clinical Medicine*, **9**, 81-86.
https://doi.org/10.4236/crcm.2020.94013

Received: March 11, 2020
Accepted: March 30, 2020
Published: April 2, 2020

Abstract

Thoracic air leak syndrome (TALS) is a rare complication of allogeneic stem cell transplant (Allo-SCT) and is associated with a poor prognosis. We report a case of a 67-year-old male, after 20 months of Allo-SCT for acute myeloid leukemia, who presented with fever and acute worsening dyspnea on a background of a 4-month history of slowly progressive dyspnea. He was initially diagnosed with parainfluenza pneumonia and later developed TALS as a result of bronchiolitis obliterans (BO) caused by chronic graft-versus-host disease (cGVHD). Herein, we highlight the importance of early recognition and treatment of non-infectious pulmonary complications of Allo-SCT.

Keywords

Thoracic Air Leak Syndrome, Pneumomediastinum, Bronchiolitis Obliterans, Graft Versus Host Disease, Allogeneic Stem Cell Transplant

1. Introduction

Allogeneic stem cell transplant (Allo-SCT) is the treatment of choice for many malignant and nonmalignant hematological disorders. Pulmonary complications of post Allo-SCT are common and are associated with a significant increase in morbidity and mortality [1] [2] [3]. Bronchiolitis obliterans (BO) is a late non-infectious pulmonary complication post Allo-SCT with a reported prevalence rate of 5.5% in one study enrolled 1145 patients. This study also identified multiple risk factors for BO and found that chronic graft-versus-host disease (cGVHD) is the most important risk factor leading to a rise in the prevalence rate to 14% [4]. Yet, the etiology of BO post Allo-SCT remains unclear.

TALS was first defined by Franquet *et al.* as the presence of extra-alveolar air in the thoracic cavity, which includes conditions such as spontaneous pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema and interstitial emphysema [5]. The mechanism of TALS is unknown but thought to be caused by the rupture of the alveoli leading to interstitial emphysema, which leads to air travel along the bronchovascular sheath to the mediastinum [6]. The fixed airflow obstruction seen in BO could lead to distal overdistention and rupture of the alveoli, which similarly permits air entry to the bronchovascular sheath. The real incidence of TALS in patients with BO remains unclear due to the lack of reported cases. The largest study in the literature estimated an incidence rate of 0.83% [7]. Multiple risk factors have been identified for TALS post Allo-SCT. The most important risk factors are grade III-IV acute GVHD, extensive cGVHD, and pulmonary invasive fungal infection [8]. Herein, we report a case of TALS in a patient with BO and describe imaging findings, pulmonary function tests (PFTs) results and clinical course.

2. Case Presentation

A 67-year-old male underwent non-myeloablative Allo-SCT for the treatment of acute myeloid leukemia (see timeline, **Figure 1**). The conditioning regimen consisted of fludarabine and total body irradiation. Both the donor and recipient were CMV seropositive with the same blood group (O positive) and a 10/10 match. The patient had successful engraftment with no evidence of graft versus host disease (GVHD) or respiratory complications in the last clinic visit to his oncologist and pulmonologist at 16 months post-transplant.

Post-transplant screening PFTs revealed an isolated reduction in the diffusing

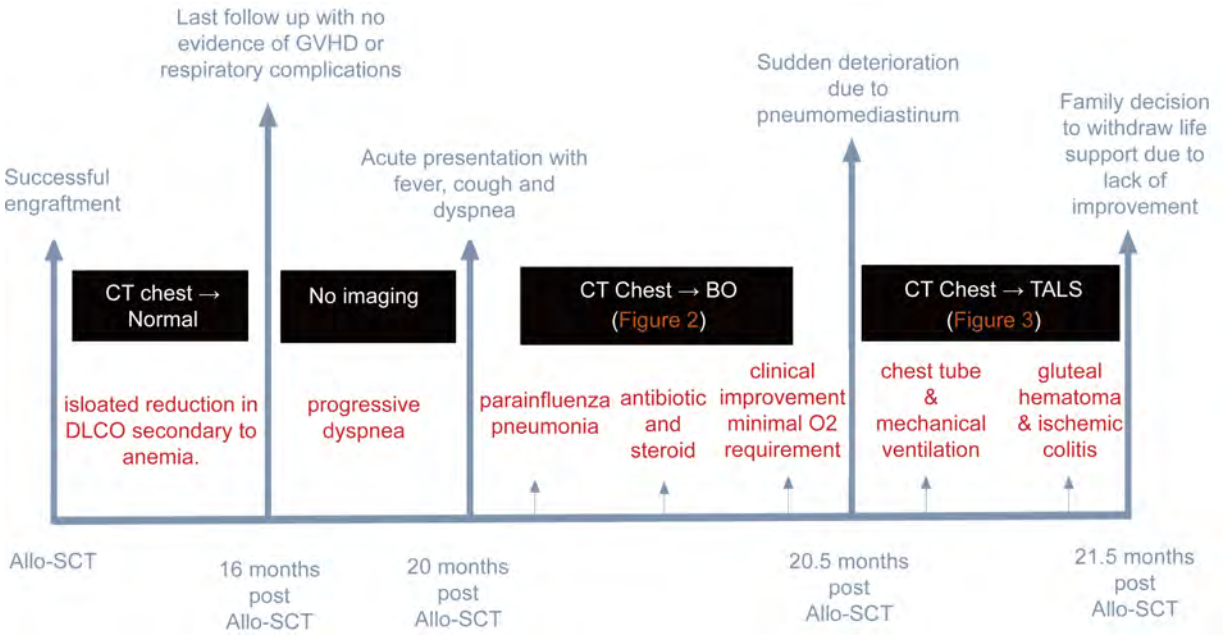

Figure 1. Timeline of important clinical information from the patient's case.

capacity of the lungs for carbon monoxide (DLCO), which was further investigated by a computed tomography (CT) scan of the chest that was normal with no evidence of pulmonary complications. The reduction in DLCO was believed to be secondary to anemia as measurements were not corrected to hemoglobin. Serial PFTs were performed to monitor changes in DLCO over time. They demonstrated a progressive reduction in total lung capacity (TLC) and an increase in residual volume (RV) to TLC ratio with no evidence of airflow obstruction.

Twenty months post Allo-SCT, the patient presented to a community hospital with a 2-day history of fever, cough and acute worsening dyspnea on the background of slowly progressive dyspnea over the last 4 months. CXR showed right middle and lower zone opacities. The nasopharyngeal swab was positive for parainfluenza virus, and blood cultures were negative. He was admitted to the hospital and treated with azithromycin and oxygen. He rapidly deteriorated in the first 48 hours, with a significant increase in oxygen requirements. A CT of the chest (Figure 2) at this time performed and showed new findings of mosaic attenuation, bronchiectasis, airway thickening and ground-glass opacities in keeping with pneumonia and new radiographic features suggestive of BO.

The patient was then transferred to our institution for further management. He was admitted to the ICU and treated with systemic corticosteroids and piperacillin/tazobactam. The patient's condition improved and stabilized over time with minimal oxygen requirement. On day 14 post admission, the patient had a sudden respiratory deterioration with an increase in oxygen requirement,

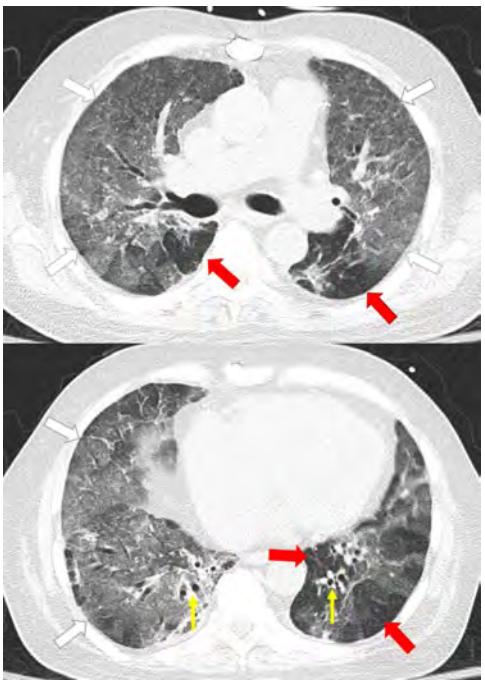

Figure 2. High-resolution CT scan of the chest showing features of BO: mosaic attenuation (red arrows), bronchiectasis and airway thickening (yellow arrows) diffuse ground-glass opacity (white arrows).

which led to urgent intubation. A chest X-ray at that moment demonstrated radiographic findings suspicious of pneumomediastinum. A subsequent Chest CT scan (Figure 3) confirmed the presence of pneumomediastinum with no definitive source of the air leak. Oral contrast study showed no evidence of esophageal perforation. Bilateral chest tubes were inserted, and mechanical ventilation was continued using lung-protective ventilation strategy. The patient continued to have a persistent air leak, and unfortunately, his ICU course was further complicated by a large gluteal hematoma and ischemic colitis. Given the complicated course and no signs of improvement after four weeks of treatment, his family decided to withdraw life support measures.

3. Discussion

Chronic GVHD is a common serious complication post Allo-SCT occurring in 60% - 80% of patients [9] [10]. It is a multisystem disease with pulmonary involvement occurring approximately in half of the patients [11]. It may manifest as BO with a fixed obstructive defect and/or bronchiolitis obliterans organizing pneumonia (BOOP) with a mixed obstructive and restrictive defect.

BO onset is usually insidious, with a non-productive cough and dyspnea. It is characterized clinically by fixed airflow obstruction and gas trapping, histologically by concentric bronchiolar lumen narrowing by submucosal fibrous tissue and radiographically by mosaic attenuation, bronchiectasis, and bronchial wall thickening [5] [12] [13]. The gold standard diagnostic modality of BO is lung biopsy. Because of the invasive nature and complications related to lung biopsy, BO is alternatively diagnosed by a combination of PFT findings, radiographic

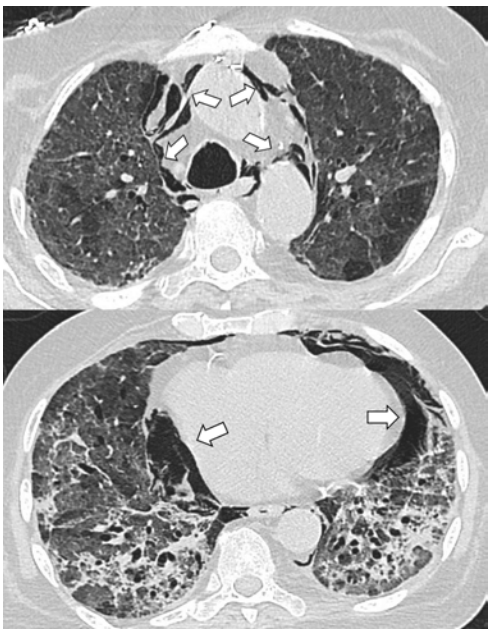

Figure 3. CT scan of the chest showing interval development of pneumomediastinum extending from the thoracic inlet to the diaphragm (white arrows).

features and at least one other distinctive manifestation in a separate organ [14]. One of the limitations in our case is the lack of a confirmatory histological diagnosis of BO and airflow obstruction on PFT. Our patient was too ill to complete these procedures, and there was no follow up for the four months preceding the presentation, which might have led to a delay in diagnosis. The initial coexistence of parainfluenza pneumonia could be a red herring. Although it could have complicated the case but is likely unrelated to TALS as the radiographic features were highly suggestive of BO, and the clinical course was not fully explained by parainfluenza pneumonia alone.

In our case, we ruled out other potential causes of TALS, such as aspergillus lung infection and pneumocystis pneumonia. Treatment of TALS in patients with BO is primarily supportive with the insertion of a chest tube and supplemental oxygen with or without ventilatory support. Once TALS developed, it is unlikely that the treatment of BO will be effective due to the irreversible damage to the bronchiole, and lung transplant will possibly be the only curative treatment if the patient survived the acute period. The development of TALS in patients post Allo-SCT is associated with a poor prognosis. Previous reports in the literature describe a high mortality rate ranging between 66.7% - 100% [7] [15]. Although our case clinical course was complicated by large gluteal hematoma and ischemic colitis, TALS with persistent air leak likely contributed to overall poor patient outcomes.

4. Conclusion

This case highlights the importance of early recognition and treatment of non-infectious pulmonary complications of Allo-SCT. Close follow up and serial assessment with physical examination, PFTs and imaging, if indicated, is warranted in this high-risk population. The early recognition and treatment of BO may reduce the risk of developing TALS, which associated with high mortality.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Case Reports in Clinical Medicine, 2020, 9, 87-95
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Clinico-Pathological Study of Invasive Fungal Sinusitis in Ibadan, Nigeria: A Case Series

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How to cite this paper: Fasina, O., Daniel, A., Ogun, G.O. and Babarinde, J.A. (2020) Clinico-Pathological Study of Invasive Fungal Sinusitis in Ibadan, Nigeria: A Case Series. *Case Reports in Clinical Medicine*, **9**, 87-95.
https://doi.org/10.4236/crcm.2020.94014

Received: March 10, 2020
Accepted: April 6, 2020
Published: April 9, 2020

Abstract

Background: Invasive fungal sinusitis is one of the less common forms of fungal infection more commonly described in North Africa and Asia. It affects healthy and immunologically competent individuals typically complicating chronic rhinosinusitis. Surgical debridement and adjuvant antifungal treatment are the mainstay of management of this condition. **Objective:** To describe the clinical presentation, pathological features and management of patients with invasive fungal sinusitis managed at a tertiary health facility, southwestern Nigeria. **Method:** Medical records of all patients with invasive fungal sinusitis managed between January 2009 and December 2018 were retrospectively reviewed. **Results:** Six patients with invasive fungal sinusitis were managed during the study period. All patients were immunocompetent and the mean age at presentation was 30.7 years ± 7.2 years. The average duration of symptoms prior to presentation was 18.5 months (Interquartile range, 67.5 months), and all six patients had orbital involvement and intracranial extension of the mass at presentation. They all had surgical debridement, and the specimens were sent for histological examination. Mycological studies carried out on two specimens isolated *Aspergillus fumigatus*as the fungal agent and all patients were started on post-operative oral antifungal chemotherapy. Five patients completed their chemotherapy and fared well with no recurrence while one patient had irregular and incomplete antifungal treatment, and developed recurrent infection before abandoning further treatment. **Conclusion:** Chronic invasive fungal sinusitis is an uncommon infection and fairly difficult to manage. However, timely diagnosis and combined surgical and medical treatment can give good outcomes in the patients.

Keywords

Clinico-Pathological Features, Ibadan, Immunocompetent, Invasive Fungal

Sinusitis, Nigeria

1. Introduction

Fungal sinusitis, broadly classified as invasive or non-invasive, is an uncommon infection, but there has been an increase in its incidence in the past few decades. Invasive fungal sinusitis can be acute or chronic in presentation. Chronic invasive fungal sinusitis (CFS), unlike acute invasive fungal sinusitis, occurs in immunocompetent, non-atopic patients who often have a history of chronic rhinosinusitis. It runs an indolent course and frequently extends beyond the sinus walls thus mimicking locally aggressive neoplasms [1] [2]. Initially asymptomatic, CFS can later present with pain, chronic headache, proptosis and cranial nerve deficits from invasion of adjacent structures. [1] Mycological studies had demonstrated majorly Aspergillus and a few Dermatiaceous species in the aetiology of the disease. [3] [4] Computed tomogram and magnetic resonance imaging are typically used to assess the extent of involvement of the paranasal sinuses and invasion of adjacent structures. Surgical debridement is required to treat this infection with extensive removal of involved tissue and bone. Antifungal chemotherapy also plays a major role in the management of the infective disease. The disease has been reported to be endemic in Sudan [5] and Northern India [4] due to the hot and dry climate in these areas which has been postulated to play a role in the aetiopathogenesis of the infection but has been rarely reported in Nigeria. To the best knowledge of the authors, there are no published reports of chronic invasive fungal sinusitis in our locality, hence this report of the cases managed at a tertiary health facility in southwestern Nigeria.

2. Method

Medical records of patients with chronic invasive fungal sinusitis managed over 10 years (January 2009 - December 2018) at a tertiary health facility, southwestern Nigeria were reviewed. Patients' clinical presentation, immune status, radiological imaging, surgical intervention, histological findings as well as treatment and outcome were studied. Diagnosis of chronic invasive fungal sinusitis was made by histopathological examination of all surgical specimens and mycological studies where possible, supported by radiological imaging in the patients. This study adhered to the Tenets of Declaration of Helsinki and informed consent was obtained from each patient for the publication of the case series.

3. Case Series

Case 1: A 35-year-old female presented with gradual protrusion of the right eye, associated with loss of vision and pain of 6 years duration. She also had spontaneous, intermittent right epistaxis with bilateral nasal blockage, hyposmia and mucopurulent nasal discharge. There were no ear or throat symptoms and she

had no features suggestive of immunosuppression. Clinical examination revealed a pale mass completely obstructing right nasal cavity, not bleeding to touch and the ear and throat appeared normal. Ocular examination revealed acuity of hand movement in the right eye, severe non-axial proptosis, and a firm mass in the supero-medial orbit. Computed Tomogram (CT) revealed an isodense mass in the right orbit andright maxillary, ethmoidal and frontal sinuses. There was an extensive aerocele into the left frontal region with direct communication with the nasal cavity. She subsequently underwent right extended lateral rhinotomy, for medial maxillectomy, right orbitotomy and bi-frontal craniotomy for excision of the tumuor and aerocele. Intraoperatively, a firm, well circumscribed irregularly shaped mass extending from the right antrum to the right ethmoid and the orbit, displacing the right eyeball laterally was excised. Histopathological examination of the tissue revealed chronic invasive fungal sinusitis. She was commenced on oral antifungal drug (Voriconazole) post-operatively with regular monitoring of the liver function and she fared well on regular follow up for about six months before she was lost to follow-up.

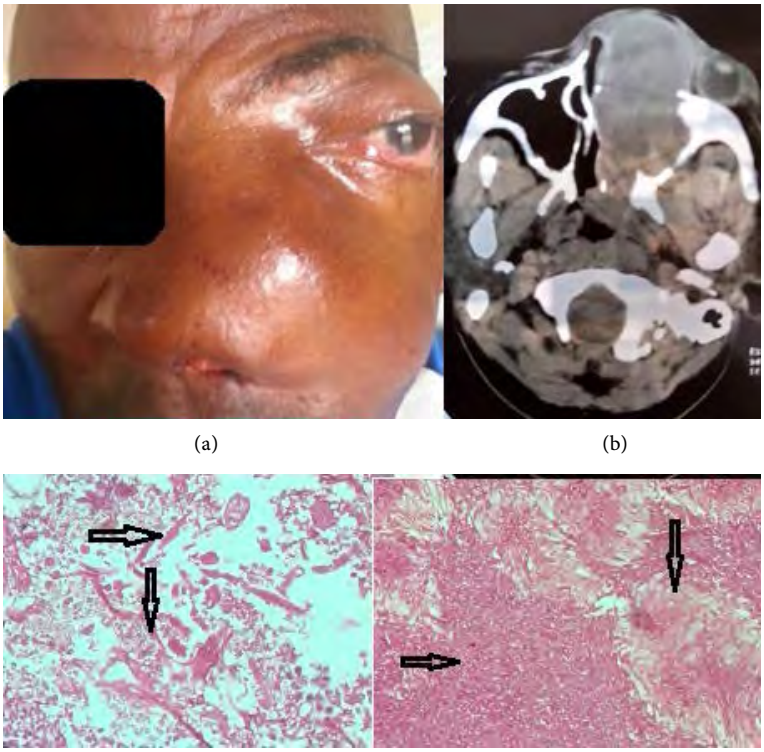
Case 2: A 24-year-old male presented with purulent left nasal discharge of a year duration and protrusion of the left eyeball of 8 months duration. There was associated nasal obstruction which was initially intermittent but later became persistent with accompanying hyposmia and frontal headache, but no fever. The proptosis was non-axial, progressive, painful and associated reduced vision. There were no features suggestive of immunosuppression in the patient and clinical examination showed reduced patency of the left nasal cavity which was filled with a brownish mass arising from its lateral wall. The mass was not sensitive, and there was no bleeding to touch. Ear and throat examinations were normal. CT scan of paranasal sinuses showed an isodense lesion in left maxillary, ethmoidal and frontal sinuses with orbital and intracranial involvement. He subsequently had left external frontoethmoidectomy, orbitotomy, and craniotomy for tumor excision. Histopathological examination of the specimen revealed an invasive fungal sinusitis. He was commenced on oral antifungal (ketoconazole) and discharged to Out-patient Clinic. However, he was irregular with the antifungal treatment and follow-up visits and re-presented with recurrent swelling for which a repeat debridement was advised, but he declined and was eventually lost to follow up.

Case 3: A 32-year-old female presented with bilateral nasal discharge of 13 months duration and protrusion of the left eye of 12 months duration. The nasal discharge was mucopurulent, occasionally stained with blood, and later associated with bilateral nasal obstruction, anosmia, snoring, hyponasal speech and frontal headache. There were no otologic or throat symptoms. Proptosis was painless, progressive and associated with loss of vision. She had no features suggestive of immunosuppression. Examination of the nose showed pale glistening mass filling both nasal cavities which appeared to be arising from lateral wall of the nasal cavity, not sensitive to probe and no bleeding to touch. Ear and throat

examinations were essentially normal. Ocular examination findings showed acuity of no light perception in the left eye with marked non-axial proptosis, chemosis and purulent discharge. CT scan of the paranasal sinuses showed isodense lesion in the left frontal and sphenoidal sinuses with destruction of orbital roof and intracranial extension. She had per nasal biopsy of the intranasal mass for histopathological examination and fungal culture and these confirmed *Aspergillus flavus* isolate from the tissue. She subsequently had bilateral external frontoethmoidectomy, bilateral intranasal antrostomy, left orbital exenteration and craniotomy with gross total tumor excision Post-operatively, she received oral Itraconazole and had repeated antral lavage with fungusol. She is presently doing well on regular follow up with no evidence of recurrence six months post-operatively.

Case 4: A 42-year-old female presented with painful progressive protrusion of her left eye of 6 months duration associated with excessive tearing. There was no nasal discharge, blockage, epistaxis or anosmia, and no otologic or throat symptoms and clinical examination of the ear, nose and throat was essentially normal. She had no features suggestive of immunosuppression. A firm swelling located in the left aspect of the glabella with inferolateral displaced left proptosis was noted on clinical examination. CT scan showed ill-defined heterogenous mass involving the medial part of the left orbit, anterior ethmoidal cells and frontal sinus, displacing the globe inferolaterally. There was destruction of the skull base with extension of the mass into the anterior cranial fossa. Surgical intervention was delayed for about 15 months due to financial constraints and the lesion had expanded to involve the skin of the forehead with discharging sinus over it. She eventually had bi-frontal craniotomy, external fronto-ethmoidectomy and orbitotomy for tumor excision. Histopathological examination and fungal culture of the specimen confirmed *Aspergillus flavus*infection and she was treated with oral voriconazole. She is on regular follow up in stable clinical condition and no evidence of recurrence eight months post-operatively.

Case 5: A 28-year-old male presented with recurrent left nasal blockage and protrusion of the left eye of 8 years duration. The nasal blockage was associated with mucoid discharge, spontaneous epistaxis, and hyposmia. There were no ear or throat symptoms and no features suggestive of immunosuppression. Clinical examination of the nose showed pale intranasal mass in both nasal cavities more on the left with thick mucoid discharge but no bleeding to touch and a firm, non-tender mass lateral to the left nostril extending to the cheek with no skin involvement. Ocular examination showed a left firm, non-tender inferior orbital mass with non-axial proptosis, superolateral displacement of the globe and reduced vision (**Figure 1**). CT scan showed left inferior orbital mixed density lesion extending to the left maxillary sinus and superiorly into the anterior cranial fossa (**Figure 1**). He subsequently had left medial maxillectomy, external fronto-ethmoidectomy, orbitotomy and trans-frontal intracranial tumor excision. Histopathological examination showed features of chronic fungal rhinosinusitis



(a) (b)

(c) (d)

Figure 1. (a) Clinical picture of the 28-year-old male with chronic fungal sinusitis involving the paranasal sinuses, orbit and anterior cranial fossa; (b) CT scan picture of the patient showing heterogeneous soft tissue mass involving the left maxillary antrum, ethmoids and the orbit; (c) Photomicrograph of the histopathologic section (Periodic Acid Schiff, ×200) of the excised tissue specimen, vertical arrow showing the yeast and horizontal arrow the hyphae; (d) Photomicrograph of the histopathologic section (Haematoxylin and Eosin, ×100) of the excised tissue specimen showing the colony of fungus (horizontal arrow) with branching hyphae (vertical arrow).

(**Figure 1**) and he was treated with oral voriconazole and has fared well six months post-operatively.

Case 6: A 23-year-old man presented with recurrent bilateral nasal blockage of 3 years duration and protrusion of the left eye of 2 years duration. The nasal blockage was initially intermittent, but progressively worsened and associated with thick mucoid discharge and anosmia. There were no ear or throat symptoms and no features suggestive of immunosuppression. The left proptosis was painless, progressive, and associated with reduced vision. Examination of the nasal cavity showed a pale glistening mass filling both nasal cavities with no bleeding to touch. Ear and throat examinations were normal. Ocular examination revealed left non-axial proptosis, .and acuity of counting fingers. Examination of the right eye showed normal findings. CT scan of paranasal sinuses showed enhancing soft tissue mass within the left frontal sinus with bone destruction and cavity expansion intracranially, and expansion into the left orbit with non-axial proptosis. There were bone destruction and extension of the mass into the ethmoid and sphenoid sinuses and left nasal cavity. He subsequently

had tumor excision through bilateral medial maxillectomy, left ethmoidectomy with sphenoidotomy, orbitotomy, and bifrontal craniotomy. Histopathological examination of the specimen revealed fungal-induced chronic rhinosinusitis, and he was treated with oral Itraconazole tablets. He has fared well and presently on regular on follow up Out-patient clinic visits 6 months post-operatively.

4. Discussion

Chronic invasive fungal sinusitis is uncommon in our environment. A hospital-based study [6] on microorganisms aspirated from the maxillary sinus in patients with sinusitis demonstrated the presence of fungi in 14.58% of patients. The fungi isolated in the study [6] were *Aspergillus flavus, Aspergillus fumigatus* and *Candida albicans*. All six cases in our series were healthy individuals without any features of immunosuppression. Chronic invasive fungal sinusitis has been shown to have a clinical course greater than 12 weeks, occurring in immunecompetent individuals, and *Aspergillus flavus*as the most common fungal agent identified indifference to acute invasive fungal sinusitis which occurs in immunecompromised individuals, and frequently implicated fungal agents include *Aspergillus* species and fungi in the order of mucorale [7]. Mould-Shalom et al in their study [8] on acute invasive fungal sinusitis reported diabetes mellitus and other immune compromise in their patients.

The mean age of our patients was 30.7 years ± 7.2 years similar to the report of Alrajhi *et al*. [9] and an equal gender distribution was also noted in our series (**Table 1**). Mostly, young, active and immunocompetent individuals of both sexes are affected by this condition [2] [9].

All the patients presented late to our facility (mean duration of symptoms, 38.5 months; range, 6 to 96 months) with orbital and intracranial involvement at presentation (**Table 2**). A slow progression of this disease has been documented, usually over months to years and patients usually present when the swelling extends to the orbit or base of the skull [1]. The typical presenting symptoms are related to chronic rhinosinusitis, upper respiratory allergies or nasal polyposis. Erosion into the orbit leads to proptosis while skull base involvement can cause chronic headache, seizures, decreased mental status or focal neurological deficits. Extension through the sphenoid sinus can give rise to orbital apex syndrome or cavernous sinus syndrome [10]. Similar to a previous report [1], proptosis was the main ocular presenting complaint in our cases.

All six patients had pre-operative contrast enhanced CT scan, which though not confirmatory, is a useful radio-imaging in defining the extent of the disease. Magnetic resonance imaging is useful in identifying involvement of the dura as well as the extent of intradural disease [2]. Chronic fungal sinusitis typically starts from the maxillary sinus on radio-imaging studies; however, it was not possible to accurately determine the paranasal sinus of origin in our patients as they presented with advanced disease and multiple sinus involvement (**Table 2**). Differentiating between invasive fungal sinusitis and malignant tumors of the

Table 1. Age and sex distribution of the patients.

Cases	Age (years)	Sex
1	35	Female
2	24	Male
3	32	Female
4	42	Female
5	28	Male
6	23	Male

Table 2. Clinical presentations of the patients.

Cases	Duration of symptoms	Eye affected	Visual loss	Paranasal sinus involvement	Nostril affectation	Intracranial extension	Follow-up period
1	72 months	Right	Yes	Max + Eth + Fr	Right	Yes	6 months
2	12 months	Left	Yes	Max + Eth + Fr	Left	Yes	3 months
3	13 months	Left	Yes	Fr + Sph	Bilateral	Yes	6 months
4	6 months	Left	No	Fr + Eth	Nil	Yes	8 months
5	96 months	Left	Yes	Max + Eth + Fr	Bilateral	Yes	6 months
6	36 months	Left	Yes	Fr + Eth + Sph	Bilateral	Yes	6 months

Max = maxillary, Eth = ethmoid, Fr = frontal, Sph = sphenoid.

paranasal sinuses is difficult both clinically and on radio-imaging, therefore, distinction is usually made onexamination of the tissue specimen at histology. The infective agents can also be identified through culture and microscopic visualization of broad, non-septate hyphae [7] [11] [12], Diagnoses of chronic fungal sinusitis was made in our series by histopathological identification of fungal organism in the tissue specimenin all six cases, and mycological studies in two patients identified *Aspergillus flavus*as the aetiological agent (**Table 3**). *Aspergillus species*are the most common agent isolated in chronic fungal sinusitis, and tissue cultures are positive in about 50% of the cases [7] [11].

Regarding treatment for chronic invasive fungal sinusitis, several authors have advocated combination therapy which includes surgical debridement with adjuvant antifungal therapy. The extent of surgery required to extirpate the disease has however been controversial, but wide aeration of the sinuses and long-term antifungal therapy is advocated [2] [13] [14]. Amphotericin B as well as the Azoles has been used as adjuvant therapy post-surgical debridement. All our patients had wide surgical debridement and the azole group of antifungals as adjuvant therapy (**Table 3**) with good response and satisfactory outcome achieved in five patients who completed their treatment. One of the patients however, was non-compliant with his medication due to financial constraints, had recurrent infection and was eventually lost to follow-up.

Our study is limited in the context that specific fungal identification by culture could not be done in four of the cases due to non-availability of the service in our facility at those periods.

Table 3. Diagnoses and drug therapy in the patients.

Cases	Diagnosis	Drug treatment
1	Histology	Voriconazole
2	Histology	Ketoconazole
3	Histology + culture	Itraconazole
4	Histology + culture	Voriconazole
5	Histology	Voriconazole
6	Histology	Itraconazole

5. Conclusion

In conclusion, chronic invasive fungal sinusitis is uncommon in our locality and affects young, active and immunocompetent individuals. Appropriate imaging studies and histopathological examination of excised tissue help in making the diagnosis of this infective disease and satisfactory treatment outcome can be achieved by effective surgical debridement and oral antifungal mediations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Case Reports in Clinical Medicine, 2020, 9, 96-106
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Cerebral Localization of Chronic Lymphocytic Leukemia Simulating Progressive Multifocal Leukoencephalopathy: The Lessons from a Case

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How to cite this paper: Sandouno, T.M., Chebrek, S., Tchonko, C., Pichancourt, G., Giovannetti, L., Zerazhi, H., Appay, R., Lepidi, H., Bachir, H., Hamaz, S., Alaoui, H.B., Serraj, K. and Slama, B. (2020) Cerebral Localization of Chronic Lymphocytic Leukemia Simulating Progressive Multifocal Leukoencephalopathy: The Lessons from a Case. *Case Reports in Clinical Medicine*, **9**, 96-106.
https://doi.org/10.4236/crcm.2020.94015

Received: February 2, 2020
Accepted: April 6, 2020
Published: April 9, 2020

Abstract

Background: Central neurological involvement is the most frequent extra hematological manifestation of chronic lymphocytic leukemia; it is multifactorial and rarely due to a cerebral localization of the disease. We report a case of cerebral localization of chronic lymphoid leukemia whose clinical and radiological aspects were very suggestive of progressive multifocal leukoencephalopathy. **Case Presentation:** A 65-year-old patient who was HIV-negative (human immunodeficiency virus), had consulted for bilateral axillary, cervical and inguinal lymphadenopathy associated with major asthenia and hyper lymphocytosis (lymphocyte count was 11 giga/l). Chronic lymphocyticleukemia with TP53 mutation was diagnosed and treatment with Ibrutinib 420 mg/day was initiated. After 2 months of treatment, the evolution was marked by the onset of neurological disorders whose clinical-radiological presentation and temporal evolution had led to the diagnosis of progressive multifocal leukoencephalopathy. In the absence of virological evidence in the cerebrospinal fluid analysis, a stereotactic biopsy of the brain lesions had been performed, making it possible to formally rule out this infectious hypothesis and to demonstrate cerebral invasion by tumour cells. Immuno-chemotherapy combining Rituximab-Cyclophosphamide-Doxorubicin-Vincristine-Prednisone-Ibrutinib (RCHOP-Ibrutinib) with intrathecal chemotherapy resulted in a very good clinical-radiological response. **Conclusion:** The appearance of neurological manifestations in the context of chronic lymphocytic leukemia must systematically lead to a search for a cerebral localization of the disease. In the absence of virological evidence in the cerebrospinal fluid, any suspicion of progressive

multifocal leukoencephalopathy in this context should lead to the histological study of brain lesions.

Keywords

Progressive Multifocal Leukoencephalopathy, Chronic Lymphocytic Leukemia, John Cunningham Virus, cerebral Localization, Ibrutinib

1. Background

Chronic Lymphocytic Leukemia (CLL) is the most common malignant hemopathy after the age of 60. It is characterized by a monoclonal proliferation of mature B lymphocytes infiltrating the bone marrow and the lymphoid organs, responsible for hyper lymphocytosis in the blood with or without tumor syndrome (lymphadenopathy, hepatosplenomegaly) [1]. Outside of these classical sanctuaries, extra-hematological tumor infiltration is a rare situation.

Although central neurological involvement is one of the most common extra-hematological manifestations in CLL, it is rarely an expression of a cerebral localization of the disease, as a variety of etiologies may be responsible for central neurological manifestation in CLL [2].

Progressive multifocal leukoencephalopathy (PML) is a central nervous system infection caused by the John Cunningham Virus (JCV) and promoted by immunosuppression. A classic complication of HIV, PML is also found in lymphoproliferative syndromes where it can be responsible for non-specific neurological manifestations with a radiological expression that is most often quite evocative [3].

Because of the highly variable therapeutic implications depending on the etiology, certainty diagnosis of neurological manifestations in CLL is of highly critical importance.

We report a case of cerebral localization of CLL whose clinical-radiological and evolutionary aspects were very suggestive of progressive multifocal leukoencephalopathy.

2. Case Presentation

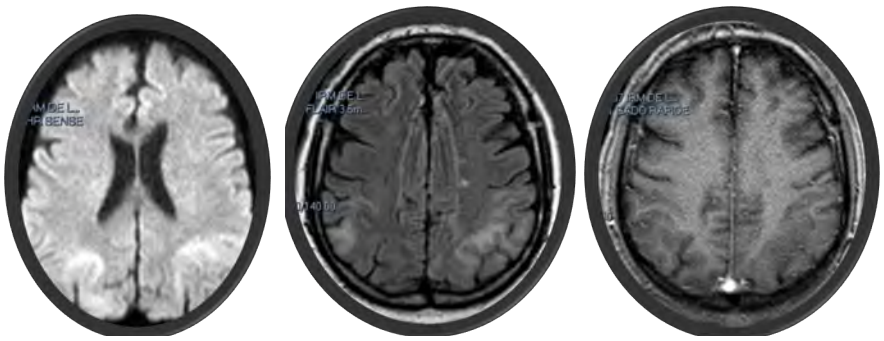
A 65-year-old diabetic patient, HIV negative, in good general condition (WHO 0), consulted in January 2018 for permanent, bilateral and symmetrical cervical, axillary and inguinal supra-centimetric adenopathies which had appeared 1 month earlier and were evolving in a context generalized asthenia without weight loss.

On clinical examination, the lymphadenopathies were isolated without hepatosplenomegaly. Blood cell count showed isolated hyper lymphocytosis at 11 giga/l. The blood smear identified small mature lymphocytes with Gumprecht shadows and lymphocyte immunophenotyping gave a Matutes score of 4/5 (CD5+/CD23+/FMC7-/CHL weak/CD79b+). The diagnosis of Chronic Lymphocytic

Leukemia B (CLL B) at stage B of Binet's prognostic classification was retained. The TP53 mutation was positive on cytogenetic analysis.

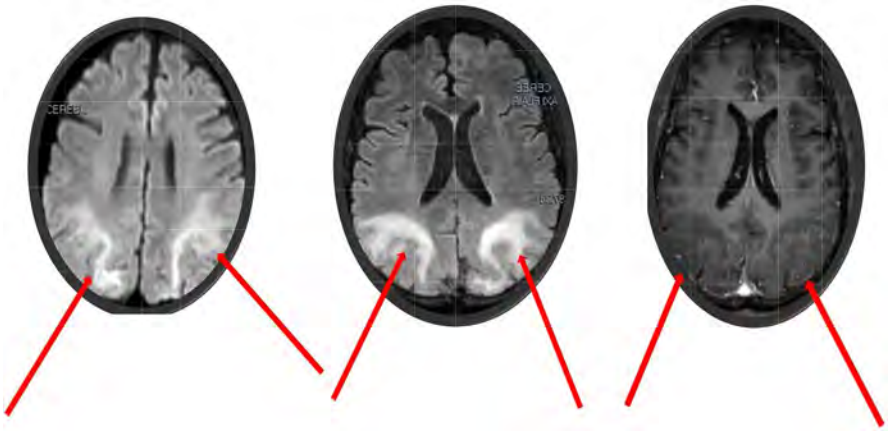
Due to debilitating asthenia, treatment for CLL was initiated; in February 2018 Ibrutinib was started at a dose of 420 mg/day. Two months later the patient was hospitalized for seizures with sudden tetraparesis. Spinal magnetic resonance imaging (MRI) was normal, but subcortical white matter abnormalities were seen on brain MRI on T1, Fluid Attenuation Inversion Recovery (FLAIR) and DIFFUSION sequences (**Figure 1**); the hepatic, renal and metabolic workup was free of abnormalities. The topography and appearance of the brain lesions, particularly the lack of contrast enhancement, associated with the clinical and therapeutic context, suggested the possibility of progressive multifocal leukoencephalopathy (PML) or herpetic meningoencephalitis. The cytological and biochemical analysis of the cerebrospinal fluid (CSF) was negative (3 elements/ mm^3); the Polymerase Chain Reaction (PCR) of JCV and Herpes Simplex Virus (HSV) was negative in CSF. Based on this PML hypothesis and despite the negativity of the PCR of JCV, Ibrutinib was discontinued and an anti-epileptic treatment was introduced and maintained over the long term to ensure effective control of seizures.

2 months after stopping ibrutinib, the patient was again hospitalized for acute confusional syndrome. A new cerebral MRI revealed an extension of the parenchymatous lesions and the appearance of marked uptake of contrast (**Figure 2**). Again, both the CSF analysis and the PCR of JCV in the CSF were negative. Hematologically, the lymphocyte count was normal, but lymph node activity was noted. The worsening of the clinical picture, the extension and the contrast enhancement of the cerebral lesions following the discontinuation of ibrutinib, led to the hypothesis of an immune reconstitution inflammatory syndrome (IRIS). Systemic corticosteroid therapy was started immediately at a dose of 1 mg/kg/day but was discontinued after 4 weeks due to the glycemic imbalance



(a) (b) (c)

Figure 1. Appearance of the first neurological symptoms. Brain MRI. Lesions are indicated by the blue arrows. (a) Diffusion sequence: bilateral parieto-occipital hyperintensity, involvement of U-shaped fibers; (b) Axial FLAIR: biparietal hypersignal with U-shaped fibers; (c) T1 axial + gadolinium: hypo-parieto-occipital signal, absence of enhancement of the lesion.



(a) (b) (c)

Figure 2. Worsening of the clinical picture. Cerebral MRI: worsening of neurological lesions. Lesions are indicated by the red arrows. (a) Diffusion Sequence: bilateral parieto-occipital hypersignal, involvement of U-shaped fibers; (b) FLAIR axial: bilateral parieto-occipital hypersignal; (c) T1 axial + gadolinium: bilateral parieto-occipital contrast enhancement, which may indicate an inflammatory response secondary to immune restoration.

and its ineffectiveness on neurological symptoms and tumor mass. 1 month later, faced with the therapeutic impasse and the lack of diagnostic evidence, we decided to perform a stereotaxic biopsy for histological study. This revealed cortical-subcortical tumor infiltration by mature lymphoid elements strongly expressing CD20, CD5, CD23 and BCL2, with perivascular or intra parenchymal topography. There was no histopathological argument for PML (**Figure 3**).

Systemic immuno-chemotherapy was instituted as follows: 4 intrathecal injections of cytarabine and hydrocortisone, 6 courses of RCHOP-Ibrutinib (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) followed by maintenance with Ibrutinib. From the third course of chemotherapy, the clinical response was spectacular, marked by a complete disappearance of the adenopathies and a neurological recovery with a resumption of walking and patient's autonomy. The control MRI at the end of the chemotherapy showed a clear regression of the brain lesions (**Figure 4**). 3 months after the end of chemotherapy, the patient is still in remission under maintenance treatment with Ibrutinib.

3. Discussion

Central neurologic involvement is one of the most common extra-hematologic manifestations encountered in CLL. It is multifactorial; it can be the direct expression of a cerebral localization of tumor lymphocytes or secondary to various infectious, inflammatory, vascular, neoplastic, metabolic or other etiologies [2]. In a study published in 2016, concerning 172 patients followed for CLL who were investigated for central neurological symptoms, approximately 80% of the cases were due to an etiology other than CLL [2]. Autopsy series revealed that the central nervous system was completely asymptomatically infiltrated in a

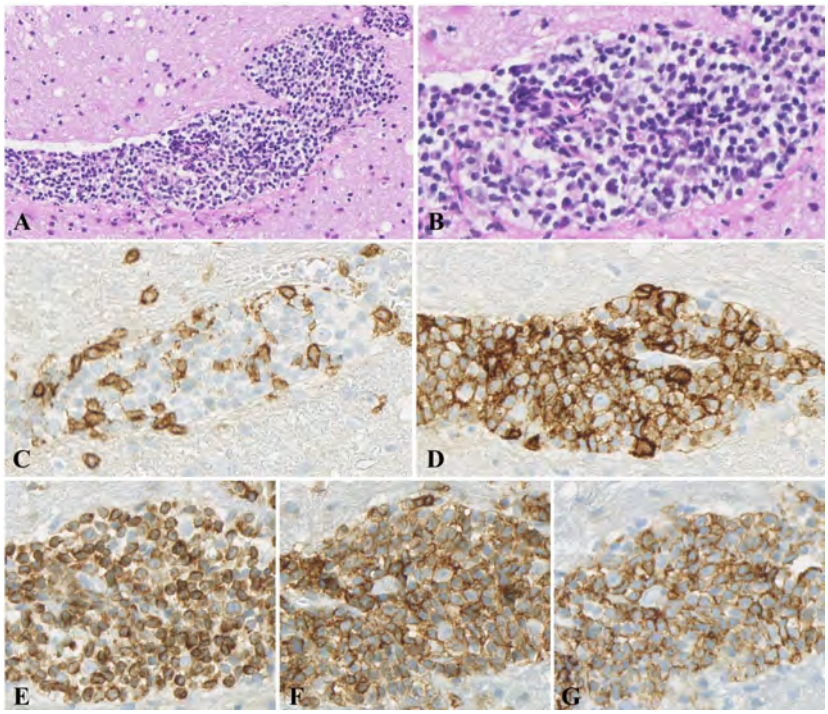


Figure 3. Lymphoid infiltrates of perivascular or intraparenchymal topography (A. HPS ×20) represented by small cells, of mature aspect, devoid of mitotic activity and atypical character (B. HPS, ×40). CD3 targets an associated reactive T lymphocyte component (C). Lymphomatous cells strongly express CD20 (D), protein Bcl2 (E), CD5 (F) and CD23 (G).

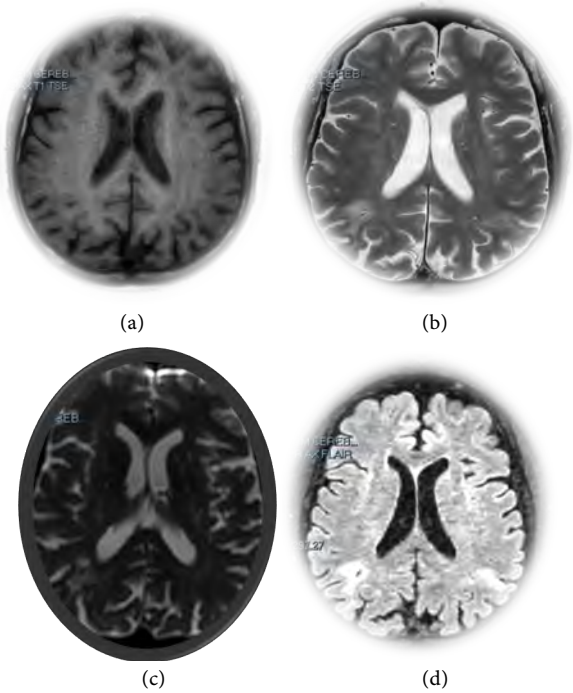


Figure 4. Brain MRI after 6 courses of chemotherapy. Significant regression of brain damage. (a) Axial T1 sequence; (b) Axial T2 sequence; (c) Diffusion sequence; (d) Axial flair.

proportion varying from 7% to 71% [4] [5]. This relatively high frequency of asymptomatic localizations on the one hand, and the considerable proportion of non-CLL etiologies on the other, justify the difficulty of the etiological approach in this context.

The clinical-radiological picture presented by our patient mainly evoked the hypothesis of PML. This hypothesis has been supported by the immunosuppression inherent in CLL and the use of a treatment that promotes apoptosis of lymphocytic cells.

PML is a central nervous system infection caused by the JCV through immunosuppression. It is frequently seen in HIV-positive patients, but can occur in patients with lymphoproliferative diseases or those treated with immunosuppressive drugs or certain targeted therapies such as Rituximab [3] [6]. In case of iatrogenic origin, it usually occurs after prolonged exposure, but rare cases of early onset are described in the literature [7] [8]. Ibrutinib, despite insufficient evidence, has been associated with cases of PML in some series [7] [9].

Cognitive and visual impairments, gait and coordination disorders, and dysarthria are the main clinical manifestations of PML, but seizures may be present in some cases [6] [10]. MRI is an essential tool in the diagnostic process, showing lesions of the subcortical white matter, in hyper signal T2 and FLAIR and in hypo signal T1. Classically, they are not enhanced after gadolinium injection and mainly concern arched fibers or U-shaped fibers with extensive and multifocal topography, which are particularly localized to posterior and temporo-parietal regions [6] [8]. The diagnosis of certainty is based on the detection of the JCV in the CSF or brain tissue. It should be noted, however, that CSF negativity does not rule out the diagnosis of PML and a histological study is essential to formally conclude [11].

Its management is not codified; no treatment has been proven for this indication, as restoration of immunity remains the only condition capable of controlling viral replication [6].

In addition to the initial clinical and radiological presentation, the occurrence of an immune reconstitution inflammatory syndrome (IRIS), which was suggested by the worsening of the clinical picture and the change in radiological aspect (extension of the lesions with contrast enhancement) after discontinuation of ibrutinib, further strengthened the diagnosis of PML initially suspected.

IRIS is an exuberant and deregulated inflammatory response to an infectious or non-infectious antigen. It results in the abrupt aggravation of a pre-existing condition or the sudden appearance of atypical clinical manifestations in the context of immune restoration. Classically found in cases of HIV infection, IRIS can occur in other pathological circumstances. It can be induced by reduction or abrupt discontinuation of immunosuppressive therapy. Corticosteroid therapy is the most commonly used treatment in this context [6] [12].

The diagnosis of PML was based on highly compatible clinical and radiological data, but we lacked virological or histological evidence of JCV imputability.

The lack of diagnostic evidence on the one hand and the rapid progression of adenopathies on the other made each of the hypotheses plausible: tumor infiltration by CLL, PML or other. It is in this context that the stereotaxic biopsy of an occipital lesion was performed; Histology revealed tumor infiltration of the white matter and the cortex by cells of known CLL with high expression of CD20, CD5, CD23 and Bcl2. However, it must be stressed that this discovery does not resolve one question: is it an extension of the disease complicating its evolution or rather an initially asymptomatic localization revealed by the therapeutic effect of Ibrutinib, when we know the capacity of this drug to cross the blood-brain barrier [13]? On the other hand, this discovery, in conjunction with our patient's CSF analysis, highlights the low sensitivity of CSF in the diagnosis of a cerebral localization of CLL. A previously cited study had shown the discrepancy between CSF cytology and cerebral histology: among 131 patients with negative cytology, 11% had a positive histology; finally among 31 patients with positive cytology, 58% had an alternative diagnosis to histology [2]. In the latter case, the presence of tumor lymphocytes in the CSF could be secondary to contamination with peripheral blood at the time of collection. As a result, CSF analysis is of low positive and negative predictive value for the diagnosis of a cerebral localization of the CLL.

Cases of CNS infiltration in CLL are described in the literature. The analysis of these cases allows us to observe a mean age of 64.5 years with a slight predominance of the male sex, a very heterogeneous clinical symptomatology with a predominance of cranial neuropathy followed by non-specific manifestations such as headache, cognitive disorders, coordination disorders or convulsions. The time from diagnosis of CLL to the onset of neurologic complications varied widely from patient to patient, ranging from a few weeks to several years; however, neurologic complications are rarely a mode of revelation of CLL [14] [15] [16]. The non-specific nature of the symptoms justifies the diagnostic delay with an average delay of 5 months. The leptomeningeal localization was the most represented, confirmed most often by the cytological study and CSF flow cytometry [14] [15]. No correlation has been established between the stage of CLL and the occurrence of neurological complications; indeed neurological localization has been diagnosed in patients in the early stage of the disease or in completely asymptomatic patients with no systemic CLL activity [17]. To date, no study has been able to identify a risk factor for neurological progression of CLL, although soluble CD27 and the study of CD49d/CD82 expression have been proposed as biomarkers of risk [16] [18]. Overall, a favourable therapeutic response was obtained [14] [15].

In addition to the common characteristics it shares with the cases described in the literature, our case has the following particularities:

- The occurrence of neurological complications during the treatment phase
- A relatively infrequent mode of disclosure compared to previously published cases.

- The hematological response under targeted therapy (normal blood count, disappearance of lymphadenopathy) coupled with the absence of tumor cells in the CSF made a neurological localization of the disease very unlikely.
- Ibrutinib, the targeted therapy used, has pharmacological properties that allow it to cross the blood-brain barrier and therefore exert its anti-tumor effect [13]; this, in view of the hematological response obtained, would make a neurological localization of CLL highly unlikely.
- The therapeutic implications are radically opposed in this context: while the diagnosis of CLL with neurological invasion requires, local or systemic chemotherapy, PML contraindicates all chemotherapy and requires immune restoration as the only therapeutic weapon recognized to date. In our case, the PML hypothesis would have been very detrimental for our patient who, let us recall, had CLL with a 17p deletion.

Furthermore, this case raises some questions: how can we explain the neurological impairment in CLL-patients in hematological response to ibrutinib, which is also an effective molecule in the CNS? How to explain the clinical picture and the morphological aspects observed on MRI?

Given the high frequency of asymptomatic CLL cerebral localizations, we believe that in our case the central nervous system was probably already silently infiltrated before the start of ibrutinib treatment. The efficacy of ibrutinib on peripheral tumor mass makes the opposite hypothesis unlikely. This invasive capacity of CLL cells is thought to be due to the dysregulation of certain integrins involved in cell migration [16].

At first glance, the morphological aspects observed on MRI would seem to correspond to a local inflammatory phenomenon as shown by MRI contrast enhancement reflecting the rupture of the blood-meningeal barrier. Should this be seen as a consequence of the action of ibrutinib? This seems implausible to us, since from a physiological point of view, the apoptosis resulting from the anti-tumour effect of ibrutinib does not induce an inflammatory reaction.

The treatment of CLL brain localizations is not codified; the few available data are empirical and relate to clinical cases or series of patients. The therapeutic strategies used vary from case to case and may or may not combine systemic chemotherapy, intrathecal chemotherapy or radiotherapy [19]. Their efficacy is variable, however there is no data to date to confirm the superiority of one strategy over another; the efficacy of Ibrutinib in this indication is found in some publications [19] [20].

In our case, we had opted for the combination of intrathecal chemotherapy with systemic immunochemotherapy, as follows: 4 intrathecal injections of cytarabine and hydrocortisone, 6 courses of RCHOP + Ibrutinib followed by maintenance with Ibrutinib. A clinical response was obtained after only 3 courses of chemotherapy: complete disappearance of superficial adenopathies, resumption of walking and patient's autonomy. The control MRI performed at the end of the chemotherapy showed a clear regression of the hyper signals. 3

months after the end of chemotherapy, the patient is doing well and is being maintained on Ibrutinib.

4. Conclusions

We infer from this case that the appearance of neurological symptoms or signs in a context of CLL should systematically evoke and search for a neurological localization of CLL regardless of the stage of the disease, its duration of progression, lymphocytes count, clinical presentation, radiological appearance or treatment received. Clinical examination, CSF studies, brain imaging and histology are key means of making the diagnosis.

In the absence of virological evidence in the CSF, any clinical and radiological suspicion of PML in the context of chronic lymphocytic leukemia should lead to the histological study of brain lesions in order to confirm the diagnosis of PML on the one hand and to rule out the possibility of a tumor localization on the other. This distinction is of critical importance because, unlike PML for which there is no effective therapy to date, there are treatments that have been shown to be effective in the management of CLL cerebral localizations.

Acknowledgments

The authors would like to thank the radiology department of the Henry Duffaut Hospital Center in Avignon for their contribution to the iconography of this article.

Consent

The patient's oral consent was obtained for the publication of this case and the associated iconography.

Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Case Reports in Clinical Medicine, 2020, 9, 107-114
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Early-Onset Type 2 Diabetes Misdiagnosed as Type 1 Diabetes in a 15-Year-Old Nigerian Girl: A Case Report

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How to cite this paper: Olamoyegun, A.M., Ala, O.A. and Saliu, O.O. (2020) Early-Onset Type 2 Diabetes Misdiagnosed as Type 1 Diabetes in a 15-Year-Old Nigerian Girl: A Case Report. *Case Reports in Clinical Medicine*, **9**, 107-114.
https://doi.org/10.4236/crcm.2020.94016

Received: January 21, 2020
Accepted: April 10, 2020
Published: April 13, 2020

Abstract

Type 2 diabetes mellitus (T2DM) is emerging as a new clinical disorder among children and adolescents. Although there is increasing prevalence of this clinical entity among adolescents worldwide, its diagnosis among Nigerian children and adolescents is still uncommon, hence, the reason many physicians still misdiagnose T2DM in adolescents as type 1 diabetes mellitus for reason of age of onset. Here, we present a 15-year old, overweight, girl who presented with history of polyuria, polydipsia and weight loss; her blood glucose level was 14.3 mmol/l, glycated haemoglobin 12.4% and glycosuria (3+), with no ketonuria or proteinuria. She was initially diagnosed as type 1 diabetes and managed with multiple doses of insulin by the pediatric team until she was later reviewed by the endocrinology unit. The diagnosis was later changed to early-onset T2DM (Youth-onset T2DM) based on a BMI of 29.75 kg/m^2, presence of acanthosis nigricans, absence of ketosis, preserved beta-cell function as shown by normal serum C-peptide levels, absence of anti-glutamic acid decarboxylase (GAD) antibodies and islet cell antibody, and also response to oral anti-diabetic agents while her insulin therapy was discontinued. Therefore, a possibility of T2DM should be suspected in childhood and adolescent with diabetes associated with overweight or obesity, relatives with T2DM and features of insulin resistance (IR) like acanthosis nigricans, hypertension, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD), hyperandrogenism, or polycystic ovarian syndrome (PCOS).

Keywords

Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Adolescent,

Misdiagnosis, Acanthosis Nigricans, Nigerians

1. Introduction

Until recently, immune-mediated type 1 diabetes mellitus (Type 1A) was the only type of diabetes considered prevalent among children, with only few cases of children considered to have type 2 diabetes mellitus or other forms of diabetes. Type 2 diabetes mellitus (T2DM), which was once considered a rare condition in childhood and adolescent population, now accounts for about 15% to 45% of all newly diagnosed cases of diabetes in children and teenagers [1] [2]. The epidemic ofT2DM in childhood and adolescent is the result of a variety of factors, the most important of which appears to be an increase in the rate of obesity in children [2].

Typically, children with immune-mediated type 1 diabetes are not overweight and have recent weight loss, polyuria, and polydipsia. However, as the population is becoming increasingly overweight, the percentage of children with type 1 diabetes who are obese is increasing [3] [4] [5]. In a comparison of youth with type 1 and T2DM, 96% of those with T2DM, versus 24% of children with type 1 diabetes, were overweight or obese at diagnosis. This epidemic of type 2 diabetes in childhood and adolescence has created difficulty in distinguishing the aetiology of diabetes in some children without advanced laboratory evaluation. Distinguishing between type 1 and type 2 diabetes in an overweight or obese adolescent, therefore, may be challenging, especially in ethnic/racial minorities, and also among developing countries like Nigeria with low incidence of type 2 diabetes among youths [6] [7]. In such patients, a detailed family history and measurement of islet auto-antibodies 65 and anti-glutamic acid decarboxylase 512 are recommended, and plasma or urinary C-peptide concentrations also may be helpful [8] [9] [10]. The differences in the treatment modalities between individuals with T2DM compared to T1DM and the profile of co-morbidities, underscores the importance that specific type of diabetes be established. Otherwise, misclassification can have serious clinical and psychosocial consequences. Incorrectly diagnosing T2DM in a young patient with T1DM could be life threatening if the situation is managed with oral diabetes medication rather than insulin. Likewise, misdiagnosing T1DM as T2DM can result in unnecessary life-long treatment with insulin, when alternative glucose lowering therapies may be more appropriate.

While there is heterogeneity in the presentation of both type 1 and type 2 diabetes, there are certain clinical features that suggest type 2 diabetes. Obesity is a hallmark of type 2 diabetes, with up to 85% of affected children either overweight or obese at diagnosis [5]. Occasionally, obesity may be masked by significant weight loss in the months or years before diagnosis. A family history of diabetes is usually present; 45% - 80% of patients has at least one parent with dia-

betes and may have a history of diabetes over several generations. Of the patients, 74% - 100% has a first- or second-degree relative with T2DMin contrast to only 5% of patients with T1DM [11]. Of note, diabetes in the parent or other relative may not be recognized until the child is diagnosed. Acanthosis nigricans is a disorder associated with insulin resistance and obesity, is common in youth with type 2 diabetes. It is described as a darkened, thick, velvety appearance to the skin found typically in folds or creases (nape of the neck, axilla, groin, and over flexor surfaces) and present in 90% of patients with type 2 diabetes and can be the most easily visible clinical indicator of insulin resistance. The frequency of acanthosis nigricans in obese adolescents or hyperinsulinemic children varies considerably by ethnicity. Up to 90% of obese or hyperinsulinemic children in Native American populations had acanthosis nigricans, whereas it was present in less than 5% of non-Hispanic white counterparts [11]. Typically, children with type 2 diabetes are usually diagnosed over the age of 10 years, that is, in the middle to late puberty. As the childhood population becomes increasingly overweight, type 2 diabetes may be expected to occur more in younger prepubertal children, hence clinicians need to be aware of this possible increasing occurrence.

2. Case Report

A 15-year old high school leaver presented at the paediatric clinic with a month history of weight loss, polyuria and polydipsia. The paternal grandmother had type 2 diabetes, the father was newly diagnosed with diabetes, and mother had systemic hypertension; her other clinical details are as shown in **Table 1**. The fasting plasma glucose (FPG) was 14.3 mmol/L, glycated haemoglobin (HbA1C) 12.4% and glycosuria (3+) but no ketonuria or proteinuria (**Table 2**).

The girl was the third of three children in a semi-affluent family with none of the siblings having diabetes. She attained menarche at the age of 12 years and had a regular menstrual cycle. Findings on examination were those of an overweight adolescent (BMI-29.75 kg/m^2), waist circumference was 96 cm, hip circumference 104 cm and waist-hip ratio was 0.92; no facial acne or evidence of hirsutism but had widespread acanthosis nigricans (at the nape of the neck, axilla, infra-mammary area, and at the groin) (**Figure 1**).

Table 1. Summary of case history.

Features	Patient
Age	15 years
Medical history at presentation	Polydipsia, Polyuria, weight loss BMI: 29.75 kg/m^2
Family history	Paternal grandmother: Diabetic Father: Newly diagnosed with diabetes & morbid obesity Mother: Hypertension & obesity
Ethnicity	Nigerian and Yoruba extraction

Keys: BMI: Body mass index.

Table 2. Clinical characteristics at presentation.

Test	Result	Normal range
Casual plasma glucose (mmol/L)	14.3	3.0 - 5.5
Glycated haemoglobin (HbA1C) [%]	12.4	3.5 - 6.4
Urinalysis; Glucose Ketone Protein	 3+ Negative Negative	
Urea (mmol/L)	4.4	3.5 - 6.5
Creatinine (µmol/L)	72	60 - 120
Anti-GAD 65 abs	Negative	
Islet cell abs512	Negative	
Serum C-peptide (ng/mL)	5.58	0.9 - 7.1
Electrolytes (mmol/L)	Sodium –136 mmol/L, Potassium –3.8 mmol/L, Bicarbonate –19 mmol/L	135 - 145 3.5 - 5.0 18 - 22
Fasting lipid profile (mmol/L)	TC: 3.0 HDL-C: 0.8 LDL-C: 2.0 TG: 0.5	3.0 - 5.5 >1. 29 <2.5 <1.69

Keys: HbA1C: Glycated haemoglobin; Anti-GAD abs: Anti-Glutamic acid decarboxylase antibodies; TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; TG: Triglycerides.

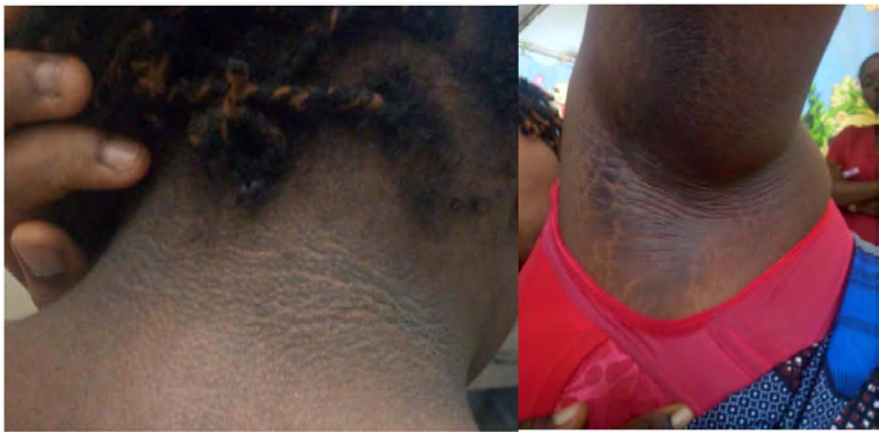

Figure 1. Acanthosis nigricans on the nape of neck & armpit.

An initial diagnosis of type 1 diabetes was made by the paediatric team based on the patient's age, and subsequently managed with multiple doses of soluble insulin. However, this initial diagnosis was revised when she was reviewed by the endocrinology unit that noted the presence of peripheral stigma of insulin resistance, i.e. acanthosis nigricans. Coupled with the patient's raised BMI, a provisional diagnosis of T2DM in an adolescent was made. Tests for antibodies to glutamic acid decarboxylase 65 (anti-GAD65) and islet cell antigen 512 (ICA512) were all negative; there was preserved beta-cell function as shown by

normal serum C-peptide levels. With the above results, a definitive diagnosis of Type 2 diabetes in adolescent was made; hence patient's insulin therapy was discontinued.

The patient and parents were adequately counseled and patient was placed on dietary control. She was advised to stop consumption of high-calorie drinks such as carbonated drinks, processed fruit juice; to reduce consumption of food with high glycaemic index such as cassava flakes, short grain rice, white bread, table sugar, etc. and to increase consumption of food with low glycaemic indexes such as vegetables, beans, porridge, grainy bread, soya beans and milk. She was also counseled to reduce her food portion and increase her physical activities with the aim of achieving, as close as possible, the weight appropriate for her age. This was done in addition to Metformin with good glycaemic response.

3. Discussion

Type 2 diabetes mellitus had always been considered a disease of older adults, while type 1 diabetes mellitus, was considered a disease of children [12]. Perhaps, this misconception is the main reason why our patient was misdiagnosed and managed as a case of type 1 diabetes, based solely on her age being. In recent times, there has been an increase in the incidence of T2DM in children and adolescents all over the world. This increase is directly proportional to a rise in prevalence and degree of obesity in adolescents, especially in regions where the diet has become more westernized with high glycaemic index [13] [14]. Increased consumption of these foods highin glycaemic index (GI) and glycaemic load (GL) lead to a resultant insulin resistance and impairment of pancreatic function.

Our patient was a 15-year old overweight female of African origin with a BMI of 29.75 kg/m^2; she had a family history of diabetes in at least two generations. Positive family history is a common finding in children and adolescents with type 2 diabetes [11]. However, diabetes in the parent or other relative may not have been diagnosed or recognized until the child is diagnosed. This was true in our patient whose father although morbidly obese, was only diagnosed on routine screening after this index patient was diagnosed of diabetes. Patients with T2DM can present in various ways, from being asymptomatic to being very ill, with or without the classic symptoms of polyuria, polydipsia, weight loss, hyperglycaemia and glycosuria with or without ketosis [15]. Many patients with T2DM whether adult-onset or early-onset usually present with one or more chronic microvascular complications of diabetes at or shortly after diagnosis [16]. However, our patient did not have any finding suggestive of such complications. Microvascular disease is the hallmark of hyperglycaemia diagnosed at a young age. In Japanese children, incipient retinopathy was detected in 36% of the cases at the time of diagnosis, and in 39% of the cases at 2 years follow-up, while microalbuminuria was observed in 39% at 2 years follow-up [17]. Hence, young people with type 2 diabetes are more likely to develop microvascular complica-

tions compared with type 1 diabetes [17]. Also, the long-term risk of cardiovascular disease in young people diagnosed with type 2 diabetes is worse than those diagnosed later in life [18]. As our patient is female, this is in keeping with female preponderance, that is, females have a higher incidence of type 2 diabetes than males, with a female to male ratio of 1.8 - 2:1.7 [5] [19]. Girls tend to reach puberty earlier and puberty is associated with fat accumulation, contributing to greater insulin resistance in girls than in boys of a similar ages; they also carry more subcutaneous fat than boys. Also, physical activity levels also tend to be lower among adolescent girls than boys and this may be adding to greater prevalence and incidence of obesity and diabetes. The peak age of onset of T2DM in children coincides with pubertal timing because the mean age at diagnosis is 12 to 16 years, with an earlier onset in girls [11] suggesting that physiological insulin resistance during puberty may play an important role. One of the markers of insulin resistance that is commonly found in adolescents with T2DM is acanthosis nigricans which our patient had. However, other markers of insulin resistance like hypertension, dyslipidaemia, polycystic ovarian syndrome (PCOS), were absent in our patient.

The primary prevention of T2DM is directed toward the obesity pandemic and involves reversing eating and entertainment trends in homes, schools, and communities that have resulted in excess caloric intake and marked decrease in energy expenditure by children and adults. The American Diabetes Association (ADA) recommends testing in overweight children and teens (BMI > 85th percentile for age and sex, weight for height > 85th percentile, or >120% of ideal body weight) who have any two of the following characteristics: type 2 diabetes in first- or second-degree relatives; African American, American Indian, Asian, Latino, or South Pacific Islander race or ethnicity; and evidence of insulin resistance or a condition associated with insulin resistance (e.g. acanthosis nigricans, PCOS, hypertension). Further, the ADA recommends that testing begins at 10 years of age or at puberty (whichever occurs earlier), that testing be repeated every 2 years, and that fasting plasma glucose testing be performed [11].

Regarding therapy, because Metformin is the only oral hypoglycaemic agent approved for paediatric use, other oral anti-diabetic agents used in adults are yet to be validated and approved for use among children and adolescents [20]. Treatment of T2DM in the paediatric population remains challenging because of the difficulty of successfully employing lifestyle changes. Hence, measures that combine dietary changes, exercise, and behavioural modification should be put in place to manage diabetes in this category of patients.

4. Conclusion

With an increasing number of reported cases of T2DM in adolescents, a high index of suspicion is needed to correctly diagnose diabetes in children with non-congruent clinical findings. Moreover, clinicians need to be aware that type 2 diabetes is not necessarily adult-onset and more education and seminars

should be conducted to sensitize the primary care physicians to give consideration to such condition in children and adolescent with diabetes. Also, it is important for clinicians to routinely screen overweight children with family history of diabetes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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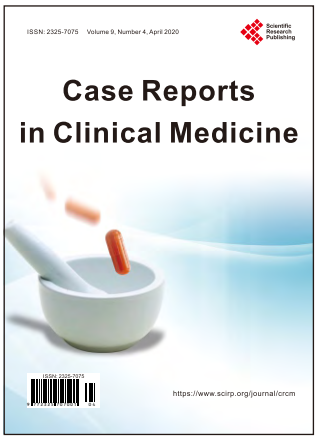

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