Case series: the rise of fungal endophthalmitis from suspected environmental contamination

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Background: A spike of 5 cases of positive culture fungal endophthalmitis occurred within a period of 30 days in patients with different working diagnosis. Investigations were initiated to look for possible causes/explanation.

Results: Five cases with different working diagnosis had positive fungal culture within a period of thirty days. Investigations showed that four out of five sampling were done in the same procedure room, and that all culture plates used were from the same refrigerator in the same procedure room. The procedure room environment was sub-optimal for procedures. A non-functioning air-conditioner created a hot and humid environment. A blowing stand-fan was used to provide air circulation during procedures. Multiple green-black-brownish spots of fungi growth were noticed on the cellulose ceiling board. The infection control team were informed and involved in investigation and rectification process, which include but not restricted to thorough disinfection procedures and air-conditioner repair. There were no longer any clinically inappropriate positive cultures reported following rectification. As patients responded well without/before starting anti-fungal therapy, we strongly believe that the clinically inappropriate positive cultures were due to environmental contamination.

Conclusion: Contamination/infection can occur via airborne pathogen transmission especially fungi, thus WHO recommended a level of <50 CFU/m^3 of air in hospital settings. A high level of suspicion should be maintained. Lab results are not absolute and clinical co-relation is of utmost importance in patient's management.

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Keywords: Endophthalmitis, fungi, air contamination, false positive culture.

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Introduction

Fungal endophthalmitis is an uncommon but severe sight-threatening ocular emergency that requires immediate treatment. Post-operative fungal endophthalmitis has a low rate of less than 1%.[1] Post intravitreal

injection fungal endophthalmitis ranges from 0% to 4%.[2,3] Endogenous fungal endophthalmitis from fungaemia has a rate of only 1.6%.[4] It is thus rare to see a sudden spike of five cases of culture-positive fungal endophthalmitis within a 30 days period, especially when these cases already had a more clinically relevant working diagnosis. Investigations were then carried out together with the hospital infection control team to identify the possible explanation or causes.

Materials and methods

This is a case series made up of five cases. We proceeded with retrospective analysis of the five cases. We investigated the first contact with the patient, history, clinical course, procedures, treatment and treatment outcome. The infection control team was also involved in our investigation, where they were involved in assessing the room with suspected contamination, which include environmental sampling for cultures and the subsequent rectification procedures. There is no conflict of interest involved in any way in the preparation of this case series.

Results

Five cases are summarised individually and listed in a chronological order. Investigation findings will also be listed, followed by solution and outcome. All positive cultures in the lab were immediately sent to Institute of Medical Research, Malaysia for continuation of culture and species identification.

First case

A 50-year-old lady with underlying bronchial asthma complained of blurring of vision in the left eye for 2 months duration associated with red eye. There was no pain, entrance of foreign body, discharge or history of trauma prior to the symptoms. She had no recent contact with any patients with red eye, but she did have TB contact history with both her parents who were previously treated as pulmonary tuberculosis 2 years ago. Her father defaulted treatment due to compliance issue, and the mother died of complication from tuberculosis infection. Visual acuity of the left eye at presentation was CF (counting finger) at 1-foot. Examination showed injected left eye, anterior chamber cells of 4+ with mutton fat keratoprecipitates and posterior synechiae. Fundus examination was hazy due to vitritis and poor pupil dilatation, with B-scan showing posterior vitreous detachment, vitritis and flat retina but no loculation. Investigations showed a raised ESR at 39mm/hr, as well as a significant Mantoux test induration of 28mm. Other infective screenings were negative. She was then treated as presumed ocular TB and was started on anti-TB treatment, planned for a total duration of at least 9 months. Following anti-tuberculosis treatment, together with topical steroid and homatropine, vision improved to CF 2-feet, but only mild improvement in anterior chamber activity, with cells 3+ and no hypopyon. She then underwent an anterior chamber tap in procedure room 6B under aseptic technique, followed by intracameral recombinant tissue plasminogen activator and moxifloxacin injection. The anterior chamber tap was sent for culture, gram staining and KOH staining, but insufficient to be processed for TB PCR. Topical moxifloxacin was added on top of the steroid following the procedure. Inflammation continued to improve, and topical steroid was reduced. However, subsequent review in clinic noted positive fungal culture (later identified as non-sporulating hyaline mold) from the anterior chamber tap. A vitreous tap and intravitreal injection of ceftazidime 2mg/0.1ml, vancomycin 1mg/0.1ml and amphotericin B 0.005mg/0.1ml was given in procedure room E16. She was also started on oral fluconazole 200mg BD, topical fluconazole 0.2% and topical amphotericin

B 0.15%. Anti-TB, topical steroids and topical moxifloxacin were continued, and she was also planned for diagnostic and therapeutic vitrectomy. Patient however was lost for follow-up since then, and defaulted admission for the surgery.

Second case

An 18-year-old girl was admitted to the medical ward and was being treated for multi-drug resistant organism Acinetobacter baumannii sepsis (blood). She was referred to the ophthalmology team for complaint of blurring of vision in her right eye. Visual acuity of the right eye was CF at 1-foot, left eye was 6/6. Right eye showed a white conjunctiva and anterior chamber has cell count of 2+ with no hypopyon. Fundus examination showed a localised and well-defined yellowish abscess measuring about 1/3 optic disc diameter covering the fovea. Vitreous showed minimal localised vitritis overlying the abscess. B-scan done showed vitreous loculation. She was treated as endogenous endophthalmitis. Vitreous tap was taken prior to the first intravitreal antibiotic injection of (ceftazidime 2 mg/0.1ml and vancomycin 1mg/0.1ml). The tap and injection were performed in procedure room 6B under aseptic technique. Following the procedure, she was started on oral ciprofloxacin 750mg BD and topical G. Moxifloxacin 0.5% and G. Dexamethasone 0.1% hourly round the clock. She was given again on day 3 of treatment, while awaiting vitrectomy. Day 6 into treatment, the vitreous tap culture came back as positive for fungi (later identified as non-sporulating hyaline mold). Patient showed clinical improvement on antibiotics alone, with less vitritis, even though the abscess size remained similar and well defined. A repeated B-scan on day 7 no longer showing any loculation. In view of the positive fungal culture, intravitreal Amphotericin B was given on top of intravitreal ceftazidime and vancomycin at day 7. Systemic anti-fungal with oral voriconazole 200mg BD was then initiated as suggested by the infectious disease team. Topical G. Amphotericin B 0.15% and G. Fluconazole 0.2% was started 2 hourly. Patient no longer receive any intravitreal injection until she undergone vitrectomy on day 13 in order to remove the sub-inner limiting membrane abscess. Repeat vitreous biopsy was taken intra-op and sent for culture. Intravitreal antibiotic and anti-fungal was given at the end of the surgery. She was kept on topical steroid, topical antibiotic, topical antifungal and systemic fungal post-vitrectomy. The repeated vitreous sampling taken intra-op in the operating theatre came back negative for any culture. Her vision recovered well since surgery with a final vision of 6/9.

Third case

A 61-year-old Chinese lady with underlying hypertension, diabetes and dyslipidemia referred from private clinic with right eye vitreous haemorrhage of unknown cause for 2 months duration. The blurring of vision was painless and of sudden onset. On examination, the vision was hand movement. The anterior segment was unremarkable. There was no fundus view with B-scan showed a flat retina with vitreous haemorrhage. The examination of the other eye was otherwise normal. She underwent right eye vitrectomy for prolonged vitreous haemorrhage. Intra-operatively, the retina and macula were flat. Inferior retinitis, temporal necrotic retinitis, vasculitis and multiple yellow-white retinal deposits resembling the clinical picture of acute retinal necrosis was observed. Vitreous sample was then taken intra-op (half-way into vitrectomy) and sent for culture, cytology, viral PCR (polymerase chain reaction) and tuberculosis PCR. Her vision immediately improved to 6/18 following the surgery, before the recurrence of vitritis on day 3 post op with viral PCR result positive for VZV

(varicella zoster virus). She was treated as acute retinal necrosis and was started on intravenous acyclovir 750mg TDS therapy day 3 post vitrectomy. Her vision improved from hand movement only to 6/9 with improving inflammation within 3 days of starting intravenous acyclovir. Her antiviral therapy was forced to stop 3 days after due to deteriorating renal function. Day 7 post vitrectomy, the same vitreous sample (positive of VZV PCR) from the operating theatre was reported to have a positive fungal culture growth, which later was identified as non-sporulating dematiaceous mold species. It is worth mentioning that even though sampling were done under aseptic technique in operating theatre, culture plates used were kept and sent to operating theatre from procedure room 6B. With the positive fungi culture, she was added on with topical anti-fungal, G. Amphotericin B 0.15% 2 hourly and G. Fluconazole 0.2% 2 hourly, despite the improvement seen on antiviral treatment. Patient continued to improve clinically with topical treatments only and steroids were gradually tapered. Unfortunately, patient developed retinal detachment 3 weeks post vitrectomy, a classical common complication of ARN, before systemic acyclovir could be restarted. She had then undergone repeated VR surgery with endolaser and silicon oil tamponade. Following the removal of silicon oil after 5 months, her right eye vision remained stable at counting finger 2-feet.

Forth case

A 59-year-old lady with underlying diabetes, hypertension and dyslipidemia, complained of progressive eye pain and redness 2 days after her right eye intravitreal ranibizumab for central-involving diabetic macula edema. She presented 15 days after the injection with a visual acuity of hand movement on the right eye. Examination showed an injected right eye. The cornea was hazy with thick hypopyon covering lower half of the anterior chamber. Fundus view was poor with B-scan showed loculations in the vitreous. A diagnosis of exogenous endophthalmitis was made and a vitreous tap was performed immediately in procedure room 6B under aseptic technique, together with intravitreal ceftazidime 2mg/0.1ml and vancomycin 1mg/0.1ml injection. Straw colored vitreous tap was obtained and was sent for culture and staining. She was then started on topical moxifloxacin 0.5% and topical dexamethasone 0.1% every hourly round the clock. Oral ciprofloxacin 750mg BD was also started. Patient underwent right eye cataract removal, vitrectomy, silicon oil tamponade and intravitreal antibiotic injection 3 days later (before culture result). Intra-operatively, extensive vitreous and pre-retinal abscess were seen and removed, with sample taken intra-op for repeat culture. Retina and macula were flat. Her topical antibiotic and steroid were continued hourly round the clock after the surgery. 2 days after surgery, initial culture result (taken in room 6B) came back with positive mold (unable to specify species) culture. Two hourly topical fluconazole 0.2% and amphotericin B 0.15% were added. 6 weeks of oral fluconazole 200mg BD was also started. Vitreous culture sent from operating theatre did not grow any organism. Patient's vision improved to 6/60 before patient subsequently developed retinal detachment with silicone oil in situ 3 months after surgery, with vision drop to hand movement only.

Fifth case

A 62-year-old gentleman with underlying diabetes, hypertension and bronchial asthma was referred from private center for continuation of care for acute post-operative methicillin- resistant staphylococcus aureus endophthalmitis. Patient underwent uncomplicated left eye phacoemulsification.

His surgery was complicated with acute post-operative MRSA endophthalmitis (vitreous culture). He was given total 3 intravitreal vancomycin injections and loaded with intravenous vancomycin in the private center, and he responded well with resolution of hypopyon. Upon admission, he presented with a left eye vision of counting finger at 1-foot. The left eye had injected conjunctiva and the cornea was edematous. Anterior chamber showed cells 2+, keratoprecipitates on endothelium without hypopyon. PCIOL was stable. There was no fundus view with B-scan showed a dense loculation near the posterior pole. A vitreous sampling for culture was performed prior to our intravitreal vancomycin. The sampling was done in procedure room 6B under aseptic technique. He was started on topical vancomycin and topical prednisolone 1% every 2 hourly on the left eye. Intravenous vancomycin 15mg/kg BD was started and planned for a total of 6 weeks as advised by the infectious disease team. 3 days after admission, vitreous culture taken on admission showed positive fungal growth identified as Geotrichum species later. Patient was then added on topical fluconazole 0.2% and topical amphotericin B 0.15% every 2 hourly in addition to the topical vancomycin and steroid. One dose of intravitreal amphotericin B 0.005mg/0.1ml was given before his vitrectomy 2 weeks later. Oral voriconazole 200mg BD was also started by the infectious disease team and was planned for a total treatment of 6 weeks but it was discontinued by our treating consultant after 12 days of treatment. Intra-operative finding during vitrectomy showed vitritis, with retina and macula flat. Vitreous sampling was done and sent for culture and staining. Intravitreal vancomycin 1mg/0.1ml and amphotericin B 0.005mg/0.1ml was given at the end of surgery. At this point of time, patient received 7 doses of intravitreal vancomycin and 2 doses of intravitreal amphotericin B. Patient was kept on topical vancomycin, anti-fungal, steroid and chloramphenicol after the surgery. Vitreous sample taken intra-operatively showed no pus cells, and no culture was isolated. Topical anti-fungal was stopped 2 weeks after vitrectomy. Patient was only on topical steroid and topical vancomycin, tapered over time. Patient's vision improved to 6/24 two weeks after the vitrectomy. Upon completion of 6 weeks of intravenous vancomycin, patient's vision further improved to 6/18. He was discharged with topical prednisolone 1% and vancomycin 6 hourly. His vision further improved to 6/6 1 month after discharge. All medications were stopped since then and he then defaulted subsequent follow ups.

From the cases above, it was clear that most of the cases above do have their own working diagnosis with strong clinical and laboratory evidence. However, the positive fungal culture had caused some distraction and minor deviation on the initial treatments which were effective, proven by clinical improvement on these patients. Though anti-fungal therapy was initiated, and mostly are incomplete therapy, the clinical course of these patients subsequently developed towards the direction of its own initial diagnosis, rather than a fungal endophthalmitis. This strongly suggests that the positive cultures were contaminations.

Discussion

Fungal endophthalmitis is uncommon compared to bacterial endophthalmitis.[1-4] The presence of five cases within a period of 30 days is extremely rare.

Four out of five cases mentioned had the positive sampling done in procedure room 6B, under aseptic technique and by different operators (ophthalmology trainees and specialist), with all five cases had the culture plates originated from procedure room 6B. While each cases above already had a working diagnosis with positive

evidence (ocular tuberculosis, endogenous bacterial endophthalmitis, acute VZV retinal necrosis, post intravitreal injection bacterial endophthalmitis and MRSA endophthalmitis), and they were responding to treatment, culture results were still pointing towards fungal endophthalmitis with the positive culture. It was already mentioned that fungal endophthalmitis is uncommon itself, it is even more rare to have a sudden surge of five cases within a range of 30 days. This led to the suspicion of contamination and thus investigations were commenced.

When contamination was suspect, it was almost always first linked with the procedure and operator. Contact contamination are usually the commonest during procedure. However, in our series, the procedure was done properly by ophthalmology trainees/ specialist and were all performed by different operators and thus the chance of improper procedure handling in each and all cases was small.

Environmental contamination was then suspected in our series, given the fact that four out of five cases had the sampling done in the same procedure room, with all the culture plates used in all five cases were kept in the refrigerator within the same room. A joint investigation was then conducted on the procedure room together with the hospital infection control team.

Following the investigation, it was noticed that the procedure is of hot and humid environment with non-functioning air-conditioner. A stand-fan was present to provide air circulation during procedure and there were no windows available. The procedure room was not reserved for ophthalmic procedures and sterile sampling, but also for ECGs, blood taking and vision taking (high volume of personnel entering the room). There was prominent fungal growth on the cellulose ceiling tiles in the room.

Figure 1: This picture shows the cellulose ceiling board in procedure room 6B. It was stained brownish by watermark, and the black-green patches were foci of fungal growth. The ceiling board was eventually replaced during rectification process.

The culture plates used in all cases were kept in the refrigerator inside the procedure room. There were also pooling of water noted around the air-conditioner vent on the ceiling and the water was taken for culture. Unfortunately, there were no direct sample taken from the fungal infested ceiling tiles for culture. Air culture was also not obtained due to the lack of appropriate equipment.

It is important to remember that fungi can survive in almost any environmental conditions, given their high adaptation ability to the environment.[5] They have multiple modes of reproduction and via multiple routes, which include air transmission via spores. Though the cultures obtained in our lab culture were mostly identified as non-sporulating species, but we must remember the basic of mycology, that certain dimorphic fungi like dematiaceous species are able to switch between sporulating and non-sporulating mode depending on the surrounding conditions like circulation, type of nutrients and temperature etc.[5] Fungi spores are almost always available in the air, both outdoor and indoor, even in conditions where no obvious sources are seen, not to mention when there

is a visible source available.[6,7]

In fact, the health threat posed by indoor fungi spores is real.[7] This has led to the development of multiple recommendations by different organizations for a safe level of indoor air fungi concentration. Due to the presence of multiple guidelines and no general consensus on which shall be the standard reference, we are referring to WHO guideline of recommendation for the acceptable level of air-borne fungi in the building published in the year 1988, where it recommends an air-borne fungi level of not more than 50CFU/m3 of air in hospital settings.[8] However, many people including healthcare personnel are not aware of its presence and importance. Air sampling was also rarely performed in our settings for it requires sophisticated air impactor for sample collection.

Studies have been conducted overseas to determine the indoor air quality of various buildings and hospitals, looking at the amount of fungi in the air. Often the fungi spore density in the air is way above the recommended level, including clean rooms in hospital.[9-12] In places with different seasons, it is during summer and autumn, where temperature is higher and more humid, had a higher concentration of air-borne fungi.[13] In tropical country like Malaysia, where the weather is persistently warm and humid all year long, air-conditioner helps reduces the indoor air fungi load.[11] Under the proper environment, fungi can easily grow on any surface. The exposure of the culture plates by just few seconds is enough for air contaminants to land, especially when the load is high in the air with turbulent air flow (which in our series, a stand-fan aiming at the procedure was present).[14]

Though unfortunately the culture came back negative of growth for samples taken from the air-conditioner vent swab and the pool of water near the air-conditioner vent (the only 2 samples taken, ceiling tiles were omitted), thorough terminal cleaning of the room was ordered by the infection control team and were done twice.

Surface cleaning (including table surface, bed, trolleys, refrigerator, floor, walls, cabinets, etc.) of the room were done twice, with each session involved the usage of Savona D2 (alcohol-based disinfectant) and Germicep (chlorine-based disinfectant). Air-conditioner were repaired promptly, and strict room temperature monitoring was initiated. The ceiling tiles infested with fungi were replaced. Curtains were also changed as part of the terminal cleaning procedure. Limitation of personnel entering the room was enforced, where the room is strictly reserved for clean and sterile clinical procedures. Thermometer was also installed in the room for continuous temperature monitoring.

Following the rectification processes, there was no longer any clinically inappropriate culture growth results obtained. This strongly suggests that the previous surge of positive cultures were contamination from the environment, supported by the fact that patients responded well before and/or without proper anti-fungal therapy.

From the experience gained through our case series, it is imperative for all clinicians to be more conscious of their clinical environment prior to any procedures, especially invasive procedures and surgeries. Environment cleanliness should be maintained by regular and thorough cleaning with the appropriate disinfectants. Disinfection should not be confined to the working area and surfaces but also electrical appliances and storages. Surrounding temperature and circulation problems should not be neglected as it contributes to transmission of airborne pathogens and may cause contamination. Most importantly, maintain high sterility during procedures to protect patients and avoid contamination. Most importantly, always remain suspicious when there is a sudden spike of inappropriate positive

cultures, as contamination can happen not only during procedure, but it also occur in, or brought into the laboratory itself.[15]

Conclusion

In conclusion, contamination of lab cultures are most commonly assumed to be contact contamination during procedures. Environmental contamination was often overlooked but it should always be suspected when a clinically inappropriate positive culture is obtained. It was always a spinal reflex to attribute any suspected contamination to improper technique during procedure. By maintaining a high level of suspicious and carrying out prompt investigations such as those demonstrated in this case series, the real cause of contamination could be identified early with proper management could be arranged. This would prevent patient mismanagement, and avoid more cases of contaminations. More importantly, management of patients should always co-relate clinical findings with history, and never solely based on lab investigations. Treatment based on lab results alone could bring more harm than benefits to patients. Strict adherence to sterile technique during sampling and procedures are no longer the only precautions which requires attention. Environmental factors like Indoor air quality and cleanliness are equally important and should never be overlooked. Transportation and storage of culture medias should be given equal emphasis. When multiple contamination is suspected, thorough investigations should be conducted and environmental factors such as humidity, air-circulation, temperature etc. should never be neglected.

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